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Chiral auxiliaries and substrate-directable reactions in asymmetric synthesis

Niyadurupola, D. Gangani

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Chiral auxiliaries and substrate-directable reactions in asymmetric synthesis

D. Gangani Niyadurupola

A thesis submitted for the degree of Doctor of Philosophy

University of Bath


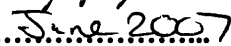
Department of Chemistry

June 2007

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Acknowledgements

Firstly I have to thank Dr. Steve Bull for his support and guidance throughout my time at Bath. Without his enthusiasm and seemingly limitless ability to see a silver lining in all of my many clouds I would never have got this far. I also have to thank AstraZeneca for my funding, my industrial supervisor Richard Wisedale and especially Paul Murray and Dave Hose from AstraZeneca Avlon for all their help and kindness.

Thanks to all the members of the SDB group, both past and present, especially Diane for being such a great friend, even from the other side of the world; Rach for being a friend from the start and who has to take some of the blame/credit for getting me into this in the first place; Matt for his chemistry wisdom and his pragmatism; Mikey for always making me smile and of course Iwan, Phil and Sonia for putting up with me in “grumpy final year” mode and getting me through it with copious amounts of coffee, biscuits and laughter. Thanks also to everyone else from the chemistry department for making these last few years so much fun and for being truly brilliant mates, there’s too many of you to mention but you know who you are.

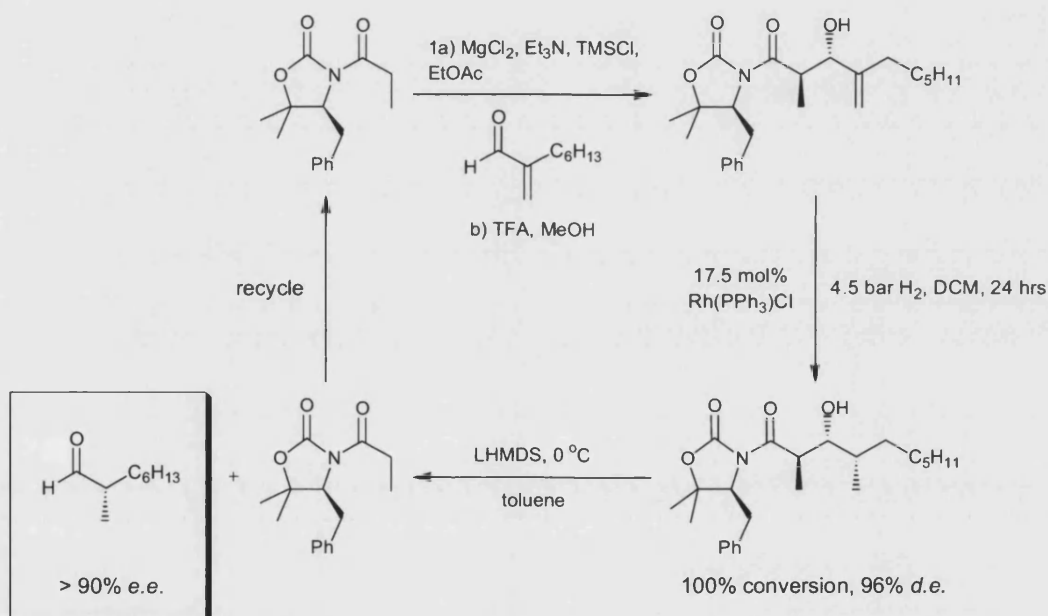
To Sarah, Gemma (and Anna), the best housemates a girl could have; thank you for everything. Thanks for being so lovely, for cooking for me and always knowing the right time to open a bottle of wine and watch Easties! I hope we stay in touch.

I also have to thank my family (Ammi, Thaththi and Aiya) without whose support I would not have been able to achieve any of this. Thank you for always being at the end of the phone, for putting up with the tears and tantrums and for trying to comprehend even when I couldn’t explain.

Lastly, but certainly not least, I have to thank Duncan. Thank you for always being there to pick up the pieces, for understanding and most of all, for looking after me. It means more to me than you’ll ever know. Here’s looking forward to enjoying all those things we never got round to. We did it!

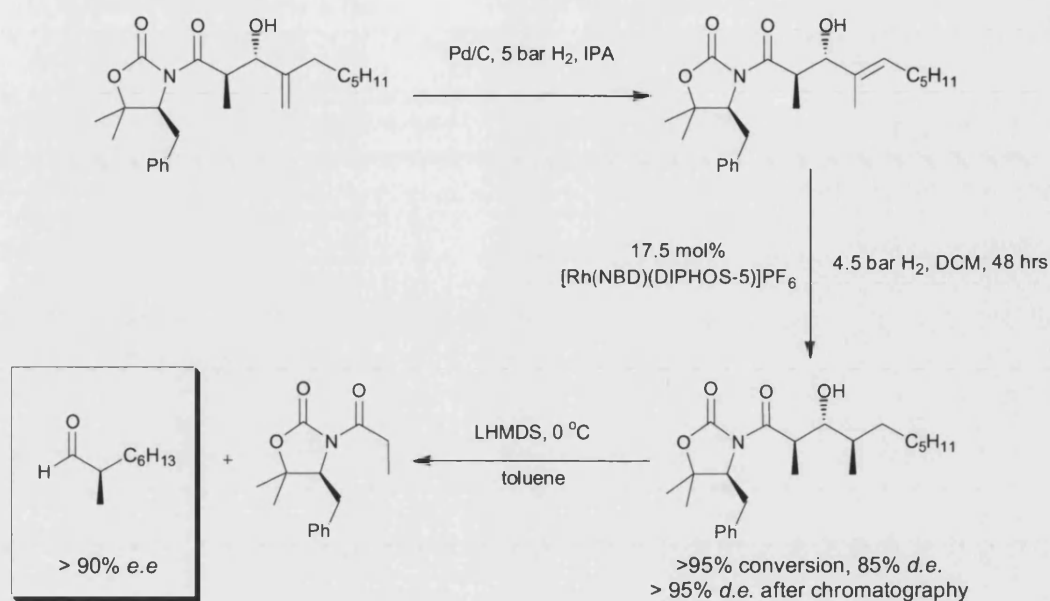
Abstract

Chiral aldehydes are useful building blocks in asymmetric synthesis. This thesis describes the development of a new way of combining chiral auxiliaries and substrate-directable reactions for the synthesis of enantiopure chiral aldehydes. This methodology relies on generation of a temporary hydroxyl stereocentre via an asymmetric aldol reaction, which is then used to direct the formation of a new methyl stereocentre via a hydrogenation reaction. The chiral aldehyde is then generated via an anionic retro-aldol reaction which destroys the hydroxyl stereocentre and regenerates the chiral auxiliary for recycling (see Scheme I).



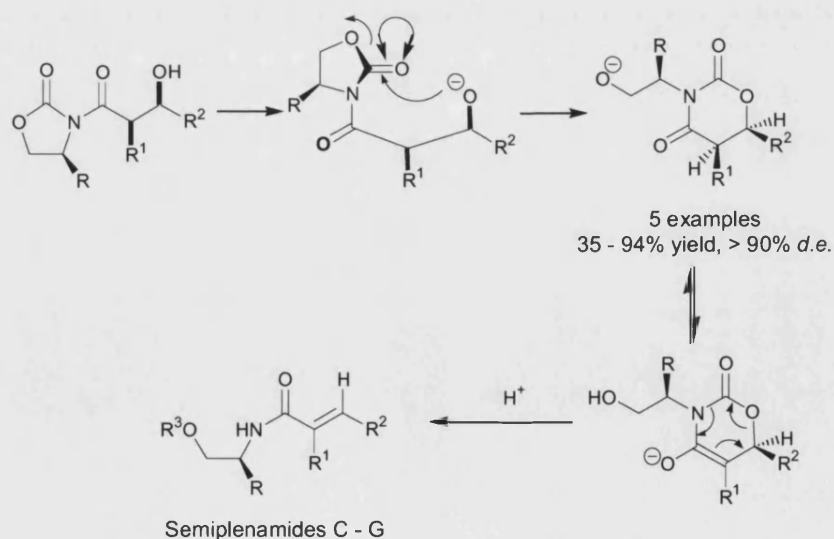
Scheme I. Strategy for the synthesis of chiral aldehydes

The hydrogenation reaction may be applied to different *syn*- and *anti*-aldol substrates using different catalysts to allow access to both enantiomers of the chiral aldehyde in excellent enantiomeric excess, which can then be derivatised in situ to afford a range of stable chiral synthons. A novel palladium catalysed isomerisation reaction has been developed which allows easy access to tri-substituted alkenes in excellent yield (see Scheme II).



Scheme II. Novel palladium catalysed isomerisation reaction to allow access to the alternate enantiomer of chiral aldehyde

By contrast Evans' auxiliary derived aldols did not undergo the same retro-aldol cleavage reaction and instead it was found that a competing cyclisation-elimination reaction could occur. This reaction pathway was exploited to synthesise a range of chiral 1,3-oxazinane-2,4-diones by treatment with 10 mol% diethylzinc, as well as a series of semiplenamides natural products by treatment with potassium *tert*-butoxide (see Scheme III).



Scheme III. Synthesis of chiral 1,3-oxazinane-2,4-diones and semiplenamide natural products by a cyclisation-elimination pathway

Abbreviations

Ac	Acetyl
Acac	Acetylacetonate
aq.	Aqueous
Atm	Atmosphere
9-BBN	9-Borabicyclo[3.3.1]nonane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1-Binaphthyl alcohol
Boc	<i>tert</i> -Butyloxycarbonyl
Bn	Benzyl
Bu	Butyl
°C	Degrees Celsius
COD	Cyclooctadiene
COSY	Correlation Spectroscopy
CI	Chemical Ionisation
D	Doublet
δ	NMR Chemical Shift
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
<i>d.e.</i>	Diastereomeric Excess
(DHQD) ₂ -PHAL	Hydroquinidine 1,4-phthalazinediyl diether
DIBAL-H	Diisobutylaluminium Hydride
DIPEA	Diisopropylethylamine
DIPHOS	Diphenylphosphino
DMA	<i>N,N</i> -Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
<i>e.e.</i>	Enantiomeric Excess
EDC	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
EI	Electron Ionisation

Abbreviations

eq.	Equivalents
ES	Electrospray
Et	Ethyl
Ether	Diethyl Ether
G	Grams
HMDS	Hexamethyldisilazide
HOBt	<i>N</i> -Hydroxybenzotriazole
HPLC	High Performance Liquid Chromatography
IPA	Isopropanol
ⁱ Pr	Isopropyl
IR	Infrared
J	Coupling Constant
LDA	Lithium Diisopropylamide
Lit.	Literature
m	Multiplet
<i>m</i>	<i>Meta</i>
M	Molar
M ⁺	Molecular Ion
Me	Methyl
Mg	Milligrams
Mp	Melting Point
m/z	Mass/Charge Ratio
NADH	Nicotinamide adenine dinucleotide
NBD	Norbornadiene
NOE	Nuclear Overhauser Effect
<i>n</i> -Bu	<i>n</i> -Butyl
NMM	<i>N</i> -Methylmorpholine
NMO	<i>N</i> -Methylmorpholine- <i>N</i> -oxide
NMP	<i>N</i> -Methylpyrrolidone
NMR	Nuclear Magnetic Resonance
<i>o</i>	<i>Ortho</i>
o-DPPFA	<i>ortho</i> -(diphenylphosphanyl)ferrocenylcarbonyl
<i>p</i>	<i>Para</i>

Abbreviations

<i>p</i> -TSA	<i>para</i> -Toluenesulfonic acid
Ph	Phenyl
PMB	<i>para</i> -Methoxybenzyl
PMP	<i>para</i> -Methoxyphenyl
ppm	Parts Per Million
Psi	Pounds Per Square Inch
Py	Pyridine
q	Quartet
RT	Room Temperature
s	Singlet
SM	Starting material
t	Triplet
TBAF	Tetrabutyl ammonium fluoride
TBS	<i>tert</i> -Butyl dimethylsilyl
<i>t</i> Bu	<i>tert</i> -Butyl
Temp.	Temperature
TES	Triethyl silyl
Tf	Triflate
THAB	Tetrahexyl ammonium bromide
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

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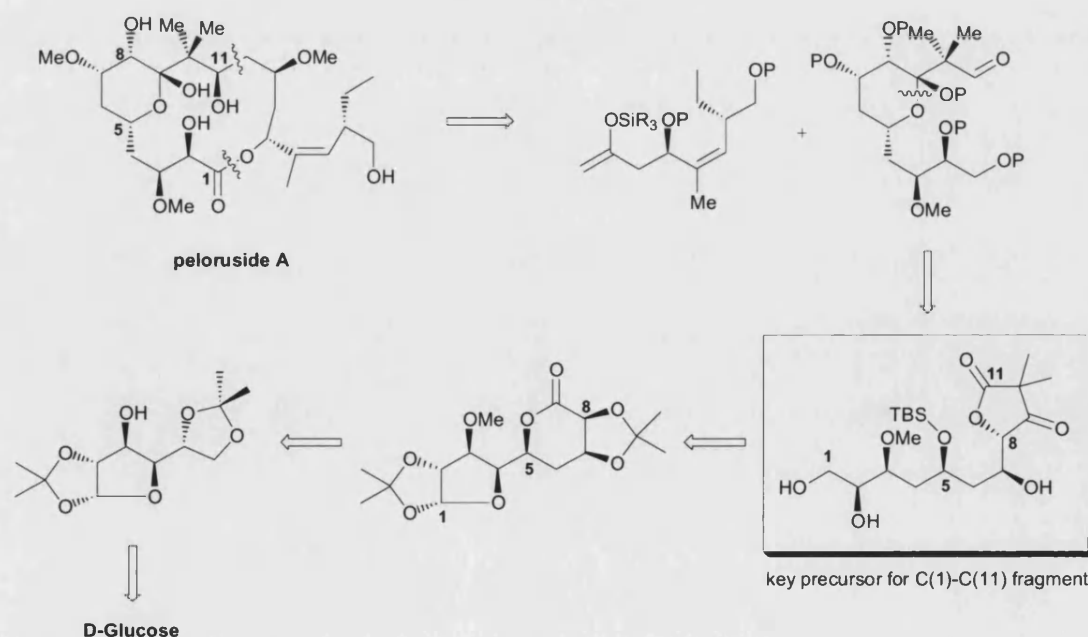
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Chapter 1: Introduction

1.1 Common methods in asymmetric synthesis

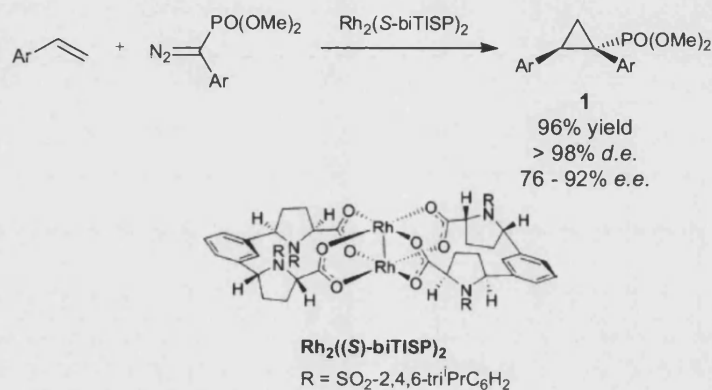
Asymmetric synthesis is the mainstay of organic synthesis. Nearly all natural products contain chiral centres and synthesis of drugs often requires control of absolute stereochemistry as receptors in the body often only recognise a single enantiomer, whilst the opposite enantiomer can sometimes produce unwanted side effects. In order to synthesize a single enantiomer of product from a prochiral precursor, the enantiotopic faces of the substrate must be discriminated so that addition to one face occurs at a faster rate than the other. There are several methods that are commonly used to achieve this, including the use of chiral pool reagents, chiral catalysis, kinetic resolutions, and chiral auxiliaries.

The chiral pool approach to asymmetric synthesis relies on using natural products as building blocks for more complicated molecules. A recent example of this is the successful synthesis of the C(1)-C(11) fragment of antitumour macrolide peloruside A, starting from D-glucose, using the strategy shown in Scheme 1.^[1]



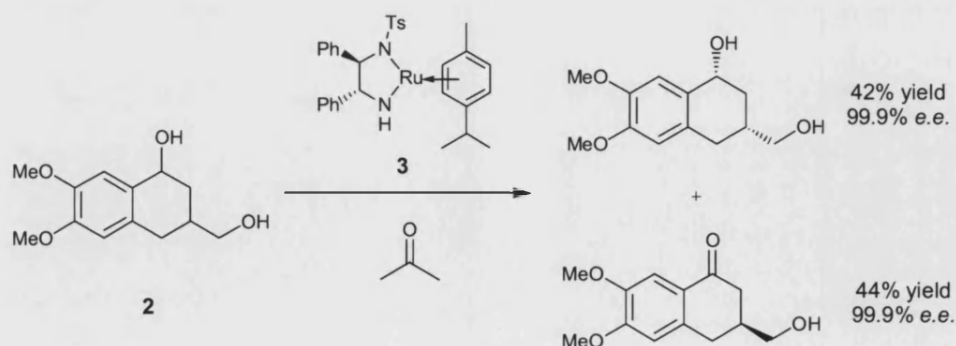
Scheme 1. Retrosynthetic analysis of C(1)-C(11) fragment of peloruside A

Chiral catalysts induce chirality by generating diastereomeric transition states of differing energies. Ideally, reaction leading to the lower energy transition state should occur much faster, leading to an enantiopure product. A recent example of this is the enantioselective synthesis of cyclopropylphosphonates **1** that contain a quaternary chiral centre catalysed by the D_2 -symmetric chiral catalyst $\text{Rh}_2((S)\text{-biTISP})_2$ (see Scheme 2).^[2]



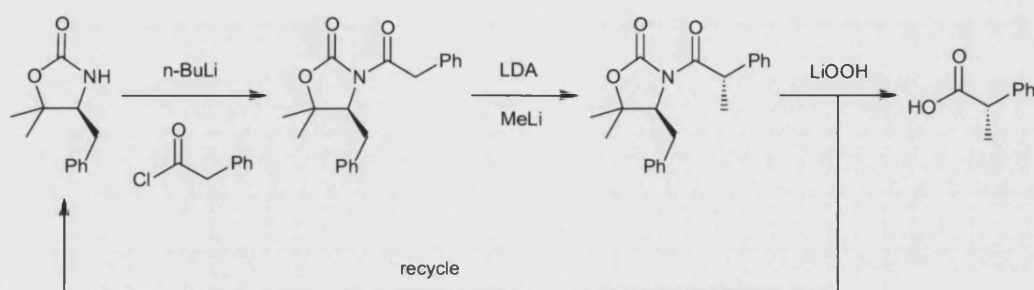
Scheme 2. Catalytic asymmetric synthesis of cyclopropylphosphonates **1** with $\text{Rh}_2((S)\text{-biTISP})_2$

Catalytic kinetic resolutions operate by reacting an enantiomerically pure reagent with a racemic substrate. One of the two enantiomers reacts more quickly allowing the enantiopure starting material and product to be separated. Masaguer recently reported the oxidative kinetic resolution of 3-hydroxymethylbenzocycloalkanols **2** by selective asymmetric hydrogen-transfer oxidation with a Noyori type ruthenium complex **3** (see Scheme 3).^[3]



Scheme 3. Kinetic resolution by asymmetric oxidation using a Noyori type ruthenium complex

Chiral auxiliaries are enantiomerically pure compounds that are attached to prochiral functional groups so that the two faces of the substrate react at different rates, with the products being diastereomers rather than enantiomers. The main requirements for a compound to act as a chiral auxiliary are that it must be readily available in an enantiomerically pure form, be easily attached to the required functional group, induce good stereocontrol and must be easily removable, preferably so that it can be recycled. This is demonstrated by the work of Davies *et al.* who reported the use of Superquat oxazolidin-2-ones for the asymmetric synthesis of chiral carboxylic acids (see Scheme 4).^[4]



Scheme 4. Chiral auxiliary approach to the asymmetric synthesis of carboxylic acids containing α -stereocentres

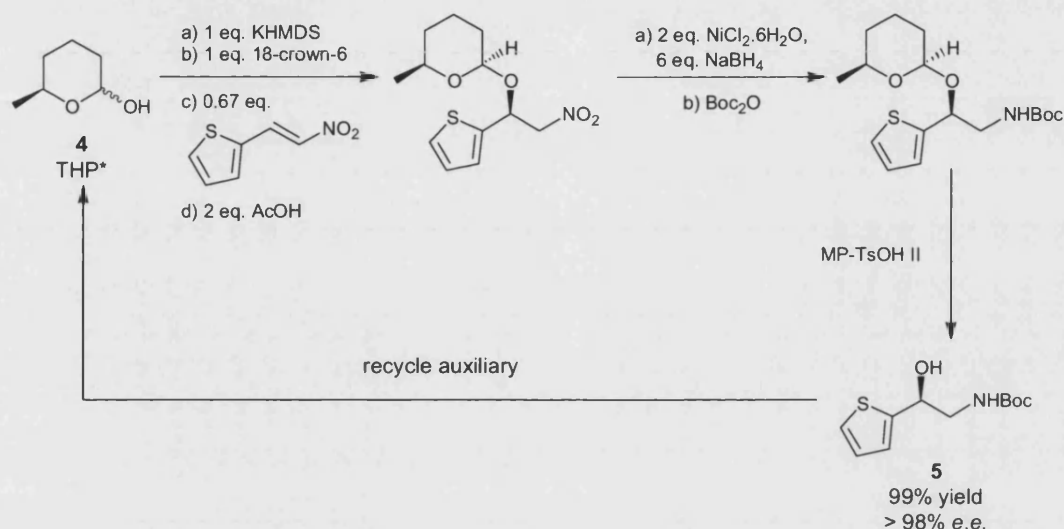
This thesis reports the development of novel methodology which combines chiral auxiliaries and substrate-directable hydrogenation reactions for the asymmetric synthesis of chiral aldehydes. Therefore, a brief report on some recent examples describing how chiral auxiliaries can be employed as powerful tools for asymmetric synthesis now follows.

1.2 Recent examples of chiral auxiliaries in asymmetric synthesis

A number of examples published in recent years serve to demonstrate the synthetic utility and efficiency of the chiral auxiliary approach for the asymmetric synthesis of chiral building blocks for natural product synthesis or drug discovery purposes.

Dixon *et al.* used a 6-methyltetrahydropyran (THP*) auxiliary **4** to control the stereochemistry of oxy-Michael additions to nitroalkenes, allowing access to enantiomerically enriched 1,2-amino alcohols **5**.^[5] The 1,2-amino alcohol motif is very

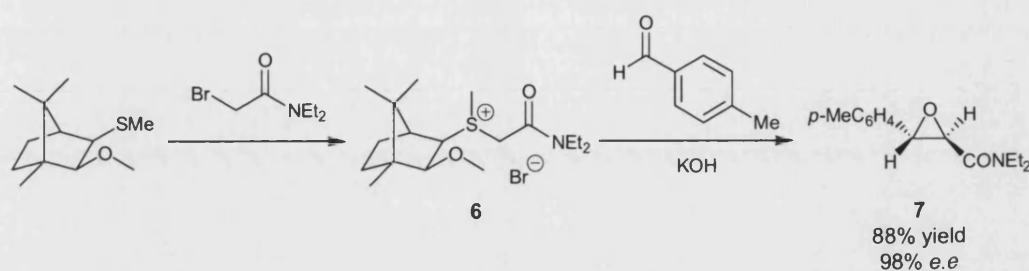
common in bioactive compounds but there are relatively few methods for its asymmetric synthesis, particularly for examples that afford products containing a stereogenic secondary alcohol centre. The alkoxide functionality of the THP* auxiliary acts as a chiral water equivalent in the reaction and directs the stereochemistry of the addition as shown in Scheme 5.



Scheme 5. Asymmetric synthesis of 1,2-amino alcohols by oxy-Michael reaction with THP* auxiliary 4

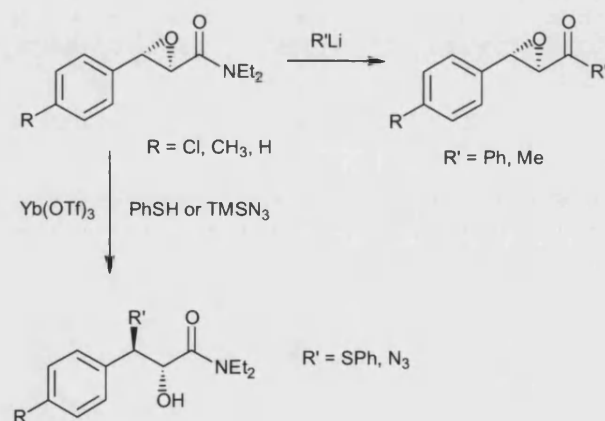
The addition of the auxiliary was shown to always favour the *cis*-THP* isomer. The process is applicable to a range of (*E*)-nitroalkenes and produces good yields and high enantioselectivity, especially with aryl, heteroaryl or alkyl R groups. This work has been further extended to allow highly stereoselective oxy-Michael additions to α,β -disubstituted nitroalkenes in good yield (66 – 99%) and excellent diastereoselectivity (> 95% at β -centre).^[6]

Camphor derived auxiliaries have been widely used in asymmetric synthesis. Aggarwal *et al.* reported the use of a camphor derived sulfonium amide salt **6** in an enantioselective Darzens reaction to yield glycidic amides **7**.^[7] This is particularly useful as it is one of the few direct routes to glycidic amides with almost complete diastereocontrol and enantioselectivity (see Scheme 6).

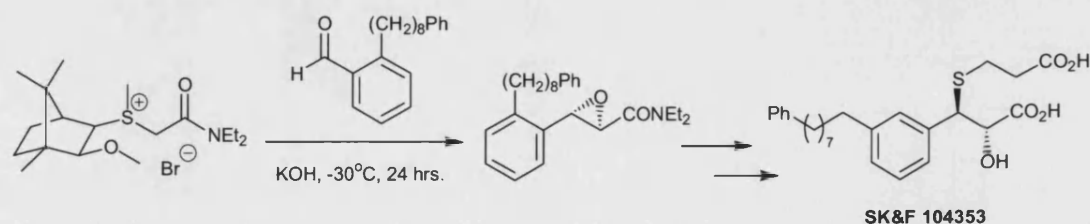


Scheme 6. Asymmetric synthesis of (2*R*,3*S*)-2,3-epoxyamides via a camphor derived sulfonium salt

The reaction was found to proceed well with a range of aldehydes including aromatic, heteroaromatic and tertiary and mono-substituted aliphatic aldehydes, although secondary substituted aldehydes gave low selectivity. The diastereocontrol was found to be always in favour of the trans isomer and the sulfide auxiliary could be isolated and reused at the end of the reaction. The group have demonstrated the utility of this reaction by carrying out further selective transformations on epoxyamides (see Scheme 7) and used the strategy in the short synthesis of SK&F 104353, a leukotriene D₄ antagonist implicated in the treatment of bronchial asthma (see Scheme 8).

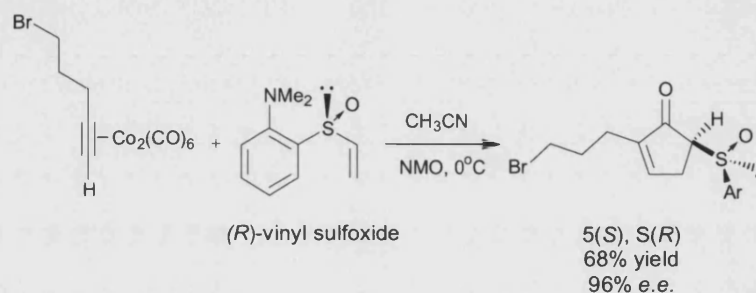


Scheme 7. Further selective transformations of epoxyamides



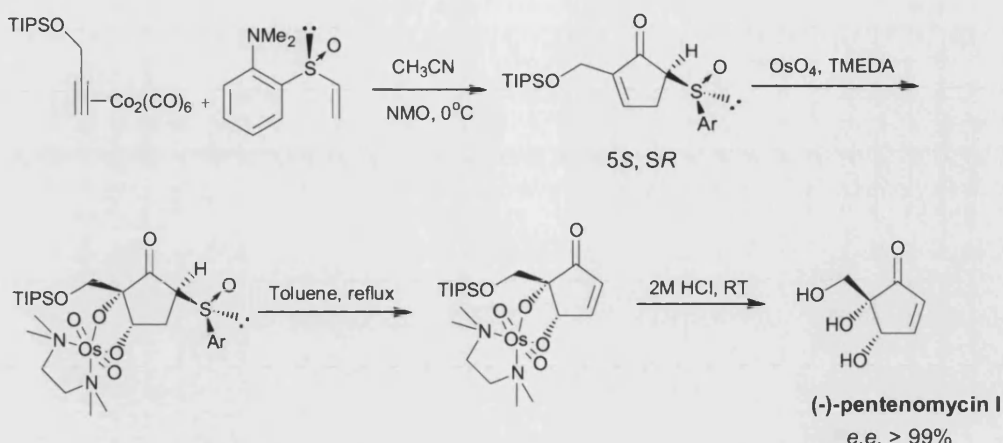
Scheme 8. Short synthesis of SK&F 104353

A more unusual auxiliary has been reported by Carretero for the asymmetric intermolecular Pauson-Khand reactions of unstrained olefins.^[8] This approach used a cobalt coordinating 2-(*N,N*-dimethylamino)phenyl vinyl sulfoxide to react with a variety of alkyne di-cobalt complexes under mild conditions with good levels of regio- and stereocontrol (see Scheme 9).



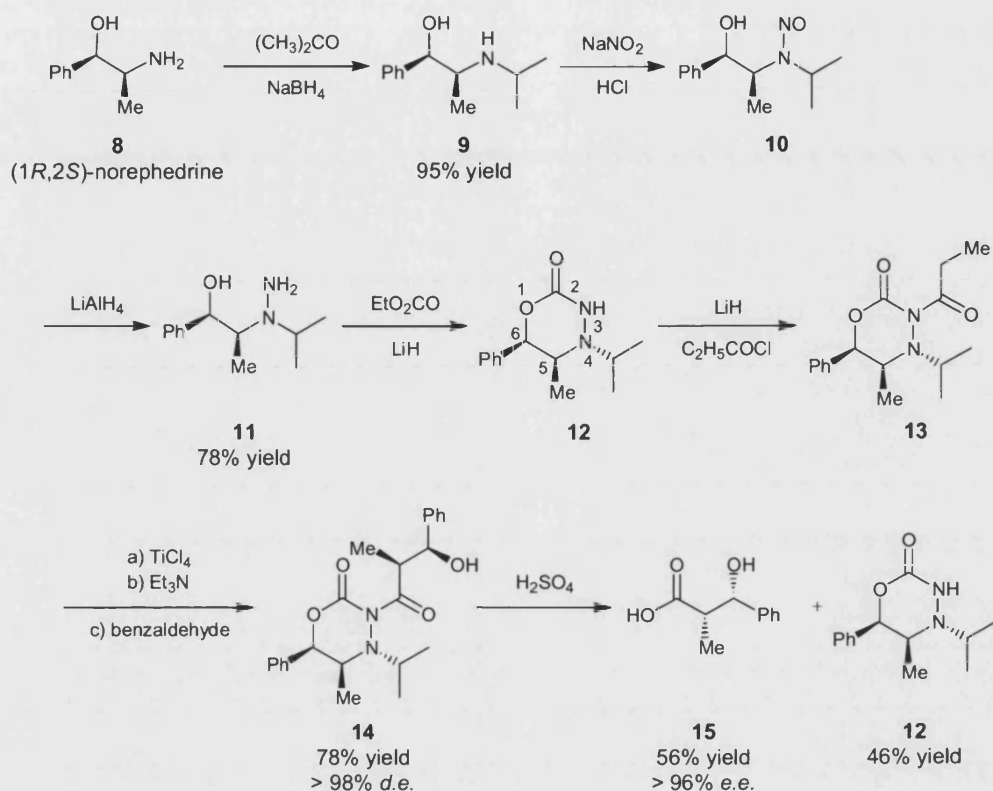
Scheme 9. Asymmetric Pauson-Khand reaction of 2-(*N,N*-dimethylamino)phenyl vinyl sulfoxide with alkyne di-cobalt complexes

The vinyl sulfoxide is easily synthesised in enantiomerically pure form and although the yields of cycloadduct are only moderate (49 – 74 %) the enantioselectivity was high (> 93% *e.e.*). The reactions were completely regioselective leading only to 2,5-disubstituted cyclopentenones, unlike many Pauson-Khand reactions of mono-substituted alkenes with terminal alkynes. The process is applicable to a range of terminal alkynes, including primary-, benzyl- and tertiary alkyl-substituted, in addition to aryl acetylenes and functionalised alkynes. The conditions are relatively mild, allowing for alkynes with a primary bromoalkyl chain to be used. However, reactions with internal alkynes such as 2-butyne, needed to be carried out at high pressure (10 Kbar) to afford any product, although stereoselectivity remains high. The versatility of this approach was illustrated by the efficient four step enantioselective synthesis of (-)-pentenomycin I antibiotic shown in Scheme 10.



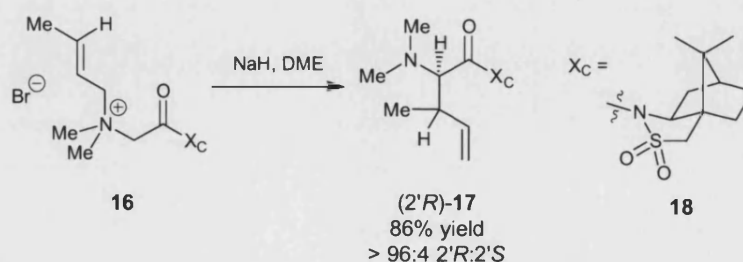
Scheme 10. Short asymmetric synthesis of (-)-pentenomycin I

Hitchcock *et al.* have reported the synthesis of chiral β -hydroxy acids via a chiral relay approach from a norephedrine derived chiral auxiliary.^[9] Reductive alkylation of (1*R*,2*S*)-norephedrine **8** with acetone and sodium borohydride afforded derivative **9** in good yield. This amine was transformed to nitrosamine **10** in quantitative yield via treatment with sodium nitrate and hydrochloric acid, before reduction to β -hydroxy hydrazine **11** in good yield. Cyclisation to give chiral auxiliary **12** was effected using lithium hydride and diethyl carbonate followed by *N*-acylation to give **13** (see Scheme 11). The acylated auxiliary **13** can undergo a titanium mediated aldol reaction with a range of aldehydes to give aldol products such as **14** in good yield (45 – 98%) and high diastereoselectivity (> 90%). Hydrolysis of **14** to give chiral β -hydroxy acid **15** and the recovered auxiliary **12** was carried out by refluxing in 6 M sulfuric acid with milder hydrolysis conditions proving unsuccessful. The configuration of the resultant β -hydroxy acid **15** confirmed that the preceding aldol reaction had afforded the non-Evans *syn* product which was proposed to arise via a Zimmerman-Traxler transition state involving a chelated Z(O)-titanium enolate. It was proposed that the chirality of the norephedrine fragment is not directly responsible for the diastereoselectivity of the aldol reaction, but rather that the stereochemistry of the methyl group at the C5 position is relayed and inverted through the conformation of the achiral isopropyl group on the adjacent nitrogen which serves to control the facial selectivity of the aldol reaction and formation of the new stereocentres.



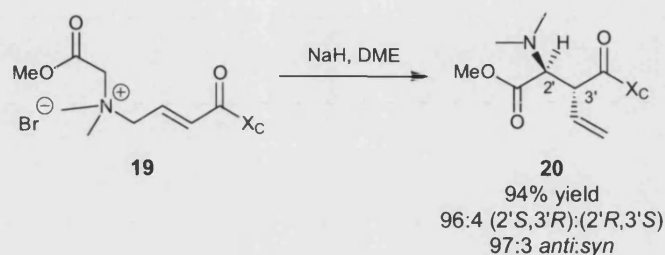
Scheme 11. Synthesis of chiral β -hydroxy acids via chiral relay from norephedrine derived auxiliary **12**

Asymmetric rearrangements are useful reactions in asymmetric synthesis due to the atom efficiency and ordered transition state of the process. Recently Sweeney *et al.* have reported the stereoselective [2,3] rearrangement of allyldimethyl ammonium ylids controlled by a camphorsultam auxiliary **18**.^[10] Thus, a range of allyldimethyl ammonium sultam ylids **16** can undergo rearrangement to afford allyl glycine derivatives **17** in good yield and excellent selectivity (see Scheme 12). The reaction proceeds well with a range of substitution patterns on the ylid including terminal alkenes which allowed access to allyl glycines which are not easily accessible by other methods.



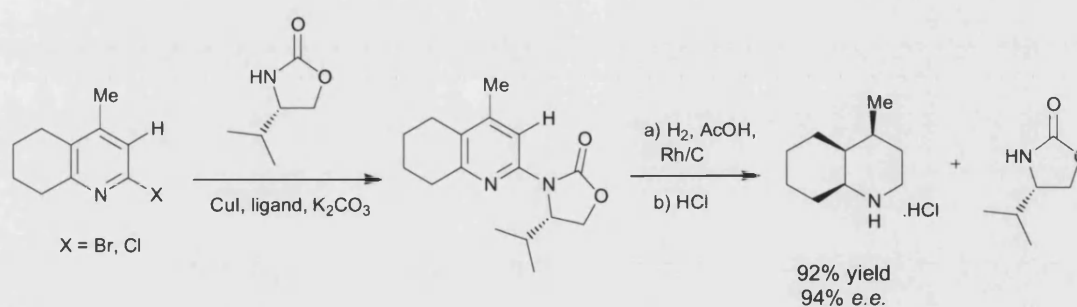
Scheme 12. [2,3] Rearrangement of allyldimethyl ammonium sultam ylids

Interestingly the auxiliary could be attached to the allylic side of the ylid to give **19** which also underwent [2,3] rearrangement with high levels of stereocontrol to afford **20** (see Scheme 13). This is exemplified by the stereoselective synthesis of (*R*)-allyl glycine in 86% overall yield and greater than 90% diastereoselectivity.



Scheme 13. [2,3] Rearrangement controlled by camphorsultam auxiliary **18**

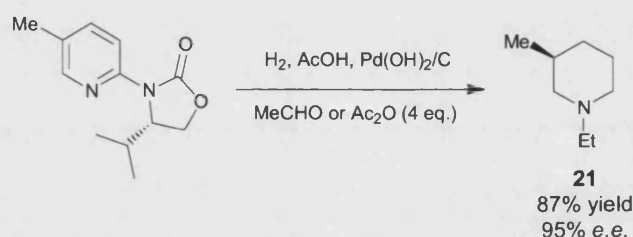
One of the most common chiral auxiliaries used in asymmetric synthesis is the Evans oxazolidin-2-one auxiliary, which Glorius *et al.* employed for the asymmetric hydrogenation of substituted pyridines.^[11] This enables the stereoselective formation of piperidines with up to four new chiral centres in a single operation, as shown in Scheme 14. The piperidine motif is common to many biologically active natural products such as alkaloids.



Scheme 14. Synthesis and asymmetric hydrogenation of oxazolidinone-substituted pyridines

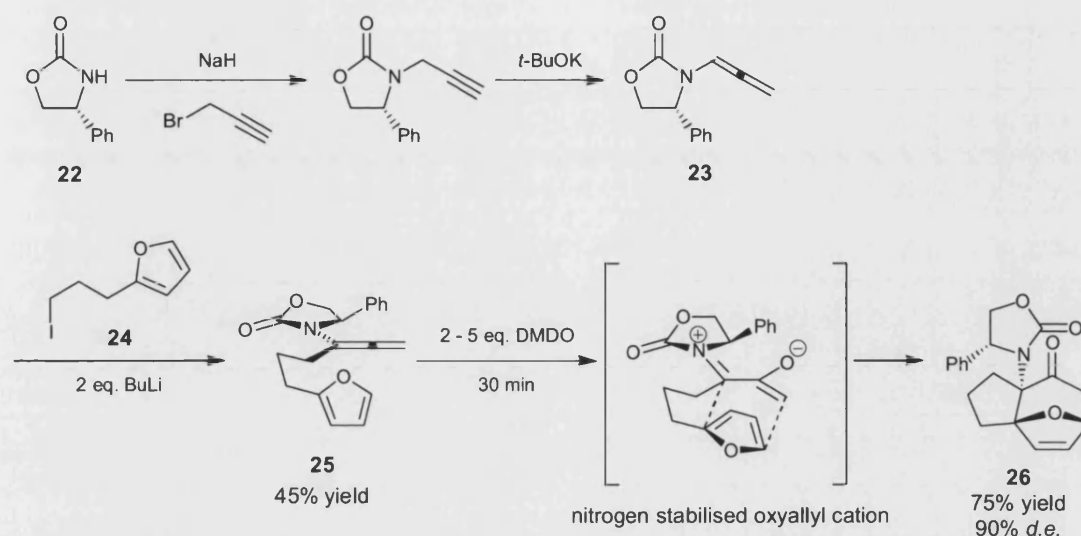
This asymmetric hydrogenation reaction occurs in good yields (63 – 100 %) and generally excellent enantioselectivity (mostly > 95% *e.e.*). The process uses fairly mild conditions, with no need for special precautions to exclude air or moisture, and is tolerant to a range of substituents on the pyridine, although selectivity is low with a methyl substituent in the R3 position. Another advantage of this process is that traceless cleavage of the auxiliary

occurs under the hydrogenation conditions, thereby combining chirality transfer and release of the auxiliary into a single step. Addition of hydrochloric acid allows separation of the more soluble auxiliary from the piperidine salt so that it can be easily recycled. This method describes an efficient and easy transformation for the asymmetric hydrogenation of heteroaromatic compounds, which has previously proved difficult. The versatility of the process was demonstrated for the formation of (*S*)-*N*-ethylpiperidines **21** as shown in Scheme 15.



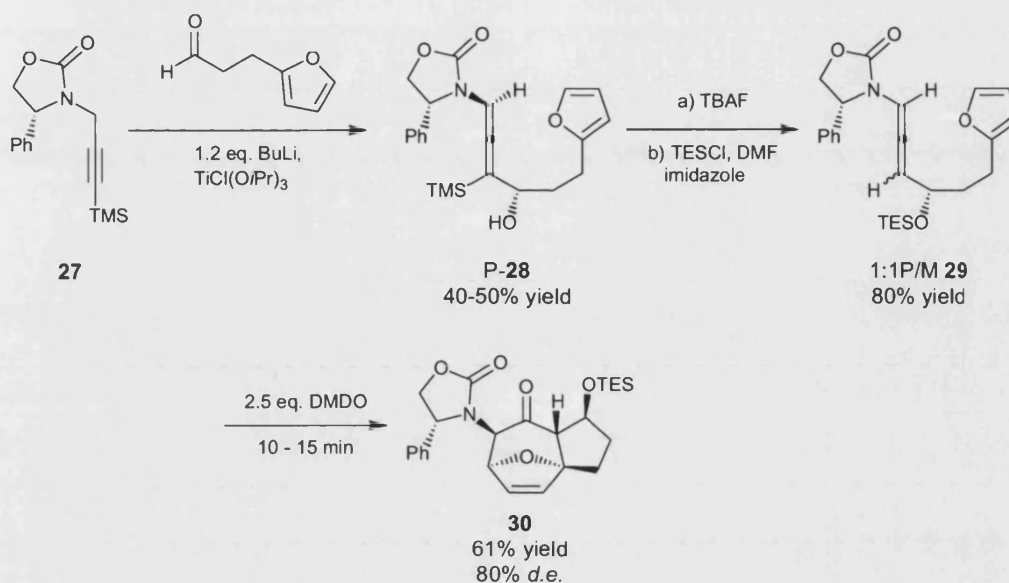
Scheme 15. Synthesis of (*S*)-*N*-ethylpiperidines via asymmetric hydrogenation

Another interesting transformation involving the Evans type auxiliary has been reported by Hsung *et al.* for the tandem epoxidation/cycloaddition of nitrogen-stabilised chiral oxyallyl cations.^[12] Allenamide **23** is synthesised from oxazolidinone **22** by alkylation followed by isomerisation with potassium *tert*-butoxide,^[13] and is then converted into α -tethered allenamide **25** by treatment with two equivalents of furan **24**. Subsequent treatment with dimethyl dioxirane (DMDO) facilitated epoxidation followed by the intramolecular [4+3] cycloaddition to give tricyclic product **26** in good yield and excellent diastereoselectivity (see Scheme 16).



Scheme 16. Tandem epoxidation/cycloaddition of α -tethered allenamide **25**

This reaction has also been extended to a range of γ -tethered allenamides. For example, allenamide **28** has been synthesised as a single diastereomer from **27** according to procedures developed by Seebach *et al.*^[14] Removal of the trimethylsilyl group led to scrambling of the allenic axial stereocentre to give **29** as a 1:1 mixture of *P* and *M* isomers after protection of the hydroxyl group with chlorotriethylsilane (see Scheme 17). However, these isomers could be cleanly separated and subsequent treatment with DMDO afforded the same isomer of cyclic product **30** regardless of the axial stereochemistry, indicating that the chirality of the allene does not govern the stereochemistry of the cycloaddition. This reaction could be extended to a range of tether lengths in the chiral allenamide and could also be carried out successfully with butadienes in place of furans in the cycloaddition reaction. This process is a useful way to synthesise chirally complex tri-cyclic compounds containing quaternary stereocentres in good yield, excellent diastereoselectivity and in very short reaction times.



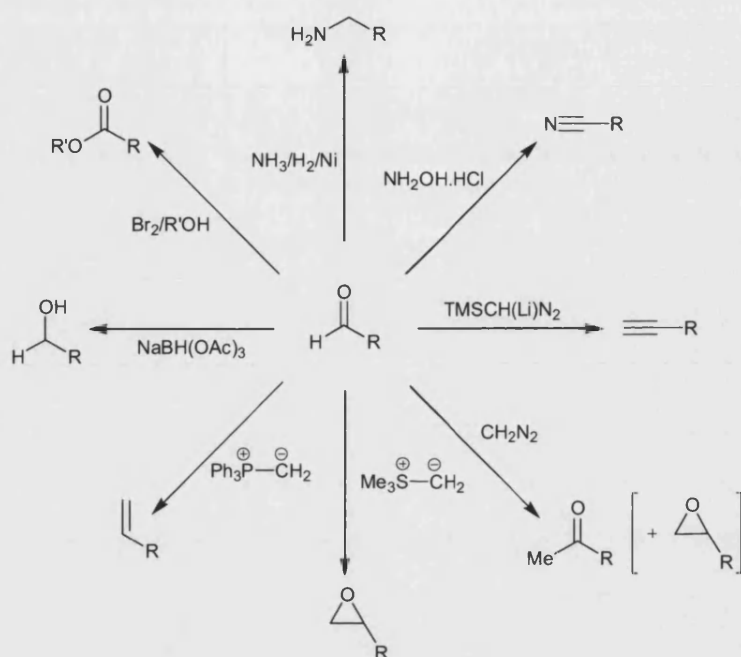
Scheme 17. Tandem epoxidation/cycloaddition with γ -tethered allenamides **29**

These examples clearly demonstrate how chiral auxiliaries can be used in a novel and efficient manner for the asymmetric synthesis of chiral products containing one or more new stereocentres. My research has been directed towards developing an efficient strategy for combining chiral auxiliaries, temporary stereocentres and substrate-directable reactions for the asymmetric synthesis of chiral aldehydes. Consequently, it is useful to consider existing methodology that is available for the asymmetric synthesis of aldehydes, and a review of this area now follows.

1.3 Strategies for the asymmetric synthesis of chiral aldehydes

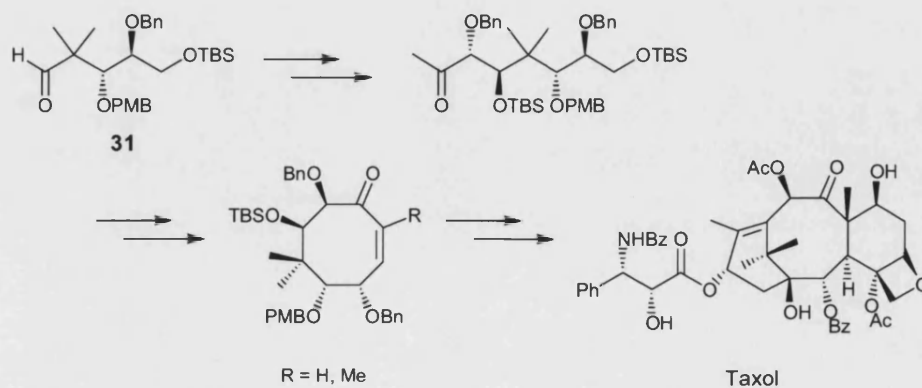
1.3.1 Introduction

Chiral aldehydes are useful building blocks in asymmetric synthesis due to the wide range of reactions they can undergo. Several one step transformations exist that can convert the aldehyde synthon into a range of other useful functionality that can be used to introduce structural diversity and chirality into complex molecules (see Scheme 18).^[15]

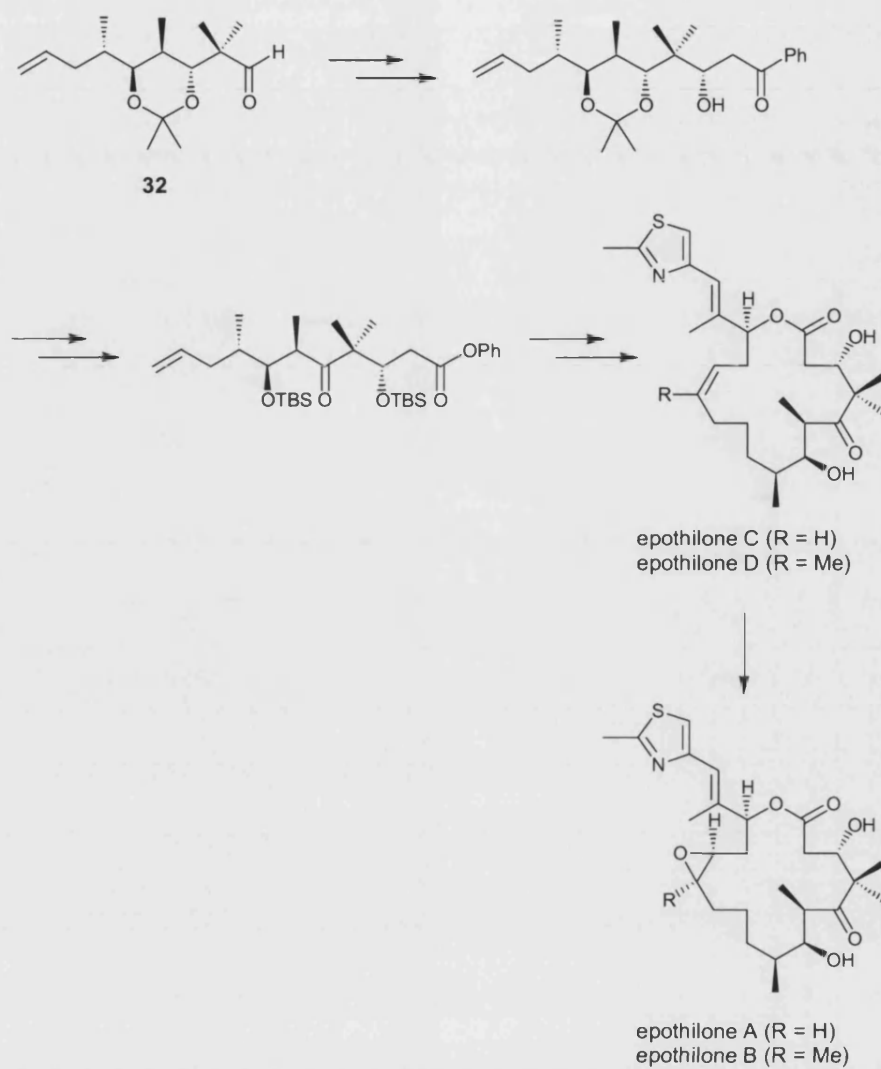


Scheme 18. Some one step transformations of aldehydes

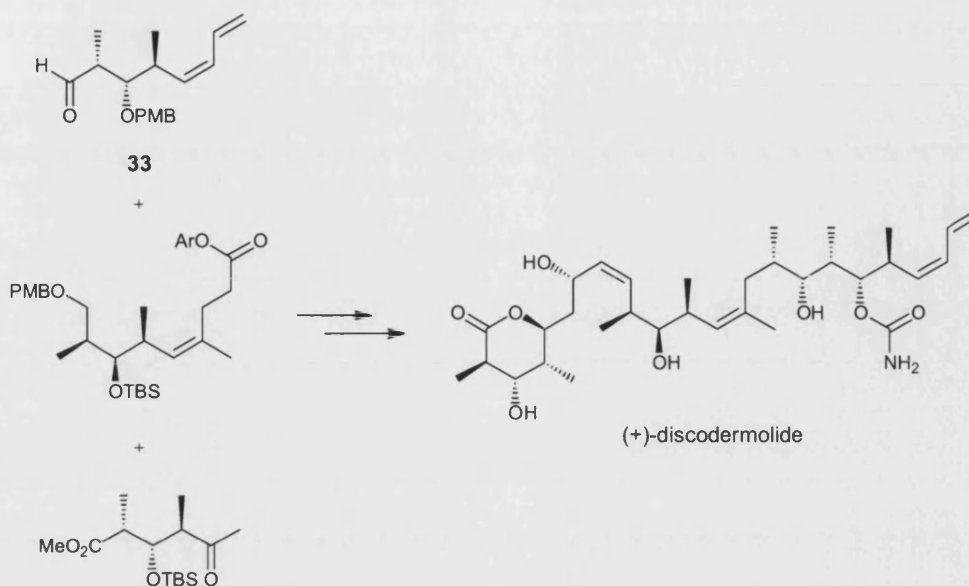
These transformations allow chiral aldehydes to be used as key intermediates for the synthesis of natural products and biologically important compounds. For example, in 1999 Mukaiyama *et al.* reported the use of chiral aldehyde **31** in the synthesis of anticancer compound Taxol[®] (see Scheme 19).^[16] The following year Shibasaki *et al.* reported the synthesis of natural products epothilones A and B from complex chiral aldehyde **32** (see Scheme 20),^[17] and in 2001 Paterson *et al.* reported the synthesis of discodermolide using chiral aldehyde **33** as a key intermediate (see Scheme 21).^[18] Both of these natural products have been shown to exhibit anticancer properties by a similar mechanism to Taxol[®].



Scheme 19. Synthesis of Taxol from chiral aldehyde **31**



Scheme 20. Synthesis of epothilones A - D from chiral aldehyde **32**

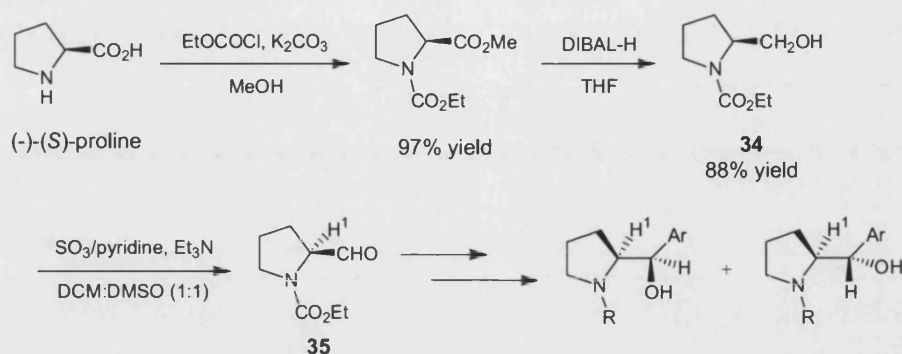


Scheme 21. Synthesis of discodermolide from chiral aldehyde **33**

These examples highlight the utility of chiral aldehydes in synthesis and therefore the importance of developing effective methods for their asymmetric synthesis.

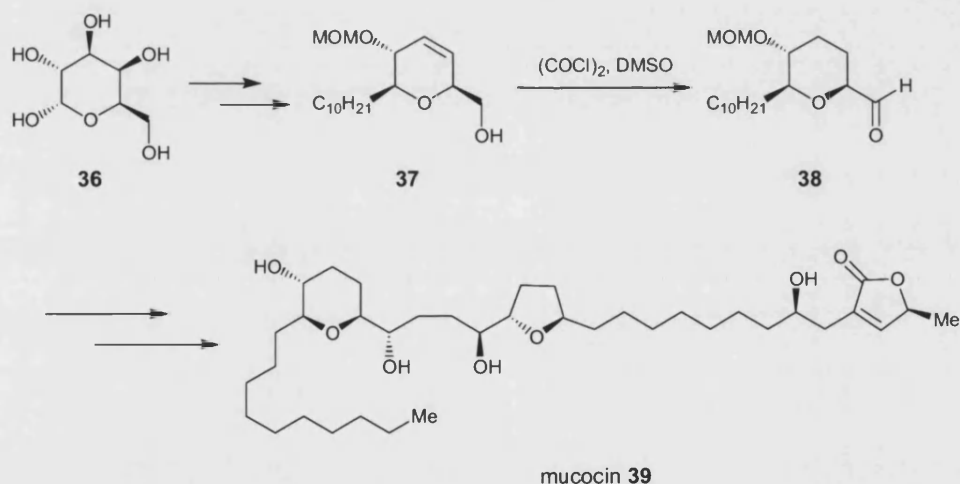
1.3.2 Oxidation, reduction and chiral pool strategies

Aldehydes are often synthesised by oxidation of primary alcohols. For example, Solladié-Cavallo *et al.* exploited this approach in their synthesis of a range of novel enantiopure (1*R*,2*S*)-*erthro*- and (1*S*,2*S*)-*threo*- isomers of aryl-pyrrolidyl alcohols from (-)-(*S*)-proline (see Scheme 22).^[19] The key aldehyde intermediate **35** was synthesised by oxidation of alcohol **34** in quantitative yield. It was found that application of Swern oxidation conditions resulted in significant racemisation due to the acidity of the stereogenic α -proton. However, this problem was overcome by using SO₃/pyridine and triethylamine in a DMSO/DCM mixture, which allowed the oxidation reaction to proceed with no racemisation. Oxidations of this type are widely used in synthesis as they prevent over oxidation of the aldehyde to its carboxylic acid.



Scheme 22. Synthesis of aryl-pyrrolidyl alcohols from $(-)-(S)$ -proline via aldehyde **35**

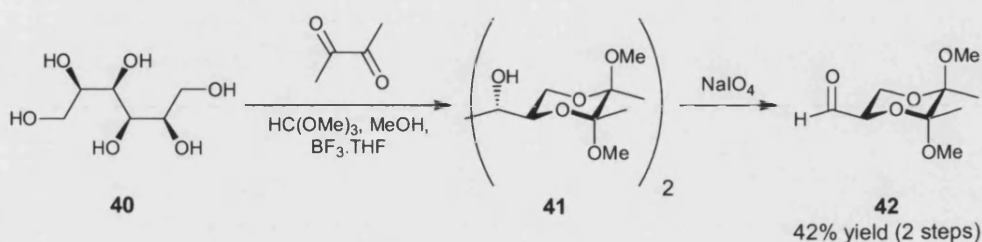
Takahashi *et al.* have exploited a “chiron approach”^[20] for the synthesis of key aldehyde **38** in their total synthesis of anti tumour agent mucocin **39**,^[21] involving Swern oxidation of alcohol **37** to give aldehyde **38** in almost quantitative yield (see Scheme 23). Although the chiron approach can be useful for asymmetric synthesis it is often inefficient due to the need to remove redundant functionality from the starting chiron.



Scheme 23. Synthesis of aldehyde **38**, the key tetrahydropyran fragment of mucocin **39**

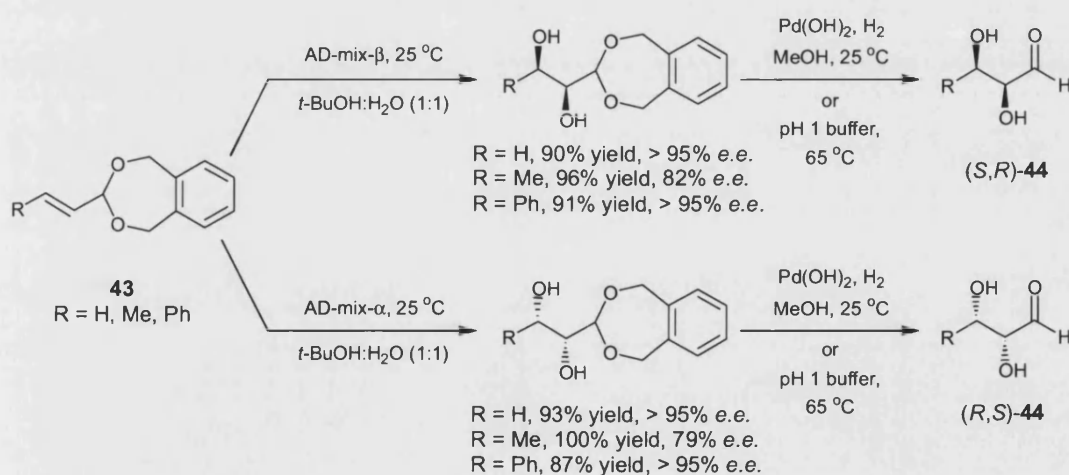
Another oxidative method for the synthesis of aldehydes involves periodate cleavage of a diol. In 2003 Ley *et al.* reported the use of D-mannitol as a cheap and convenient starting material for the synthesis of chiral butane-1,2-diacetal-protected glyceraldehyde **42**.^[22] D-mannitol **40** was treated with butane-2,3-dione and trimethyl orthoformate in the presence of a catalytic amount of boron trifluoride tetrahydrofuran to yield the protected mannitol

derivative **41**. This diol was oxidatively cleaved with sodium metaperiodate to afford glyceraldehydes derivative **42** in 42% yield over two steps which can be used as a building block in natural product synthesis (see Scheme 24). Sugars have often been used as chiral synthons for the synthesis of chiral aldehydes in a similar way.^[23]



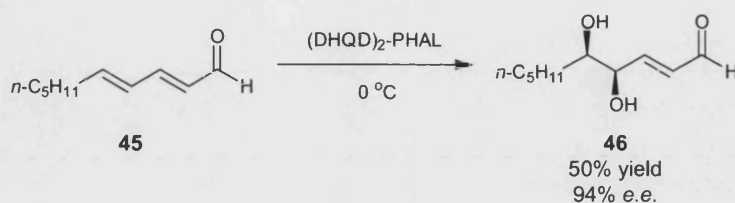
Scheme 24. Synthesis of butane-1,2-diacetal-protected glyceraldehyde **42** from D-mannitol **40**

Sharpless *et al.* have reported the use of the osmium catalysed asymmetric dihydroxylation procedure to synthesise a range of chiral dihydroxyaldehydes **44** from acetal protected α,β -unsaturated aldehydes **43** in good yield and enantioselectivity as shown in Scheme 25.^[24] The acetal protecting group could be easily removed by hydrogenolysis or acid hydrolysis without racemisation of the stereocentres and the resultant aldehydes could then be subjected to an enzyme catalysed aldol reaction to afford a range of carbohydrate products.



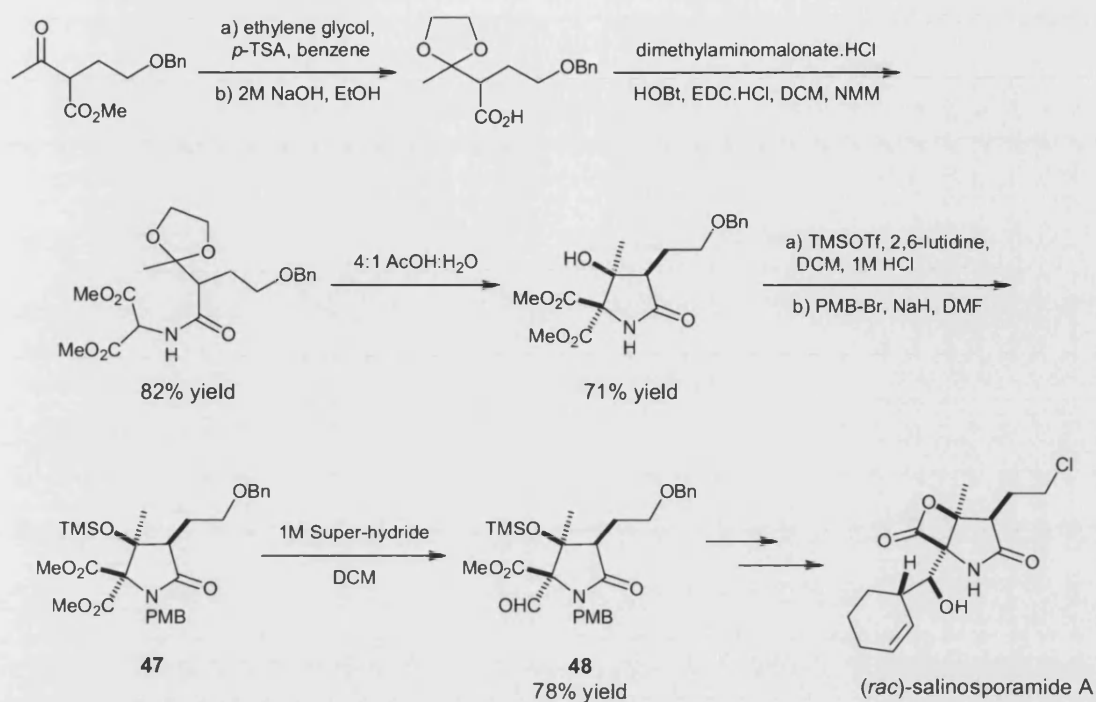
Scheme 25. Synthesis of dihydroxyaldehydes by osmium catalysed asymmetric dihydroxylation

A similar dihydroxylation strategy was used for polyunsaturated aldehyde **45** whose γ,δ -alkene functionality was selectively dihydroxylated to afford dihydroxyaldehyde **46** (see Scheme 26).^[25]



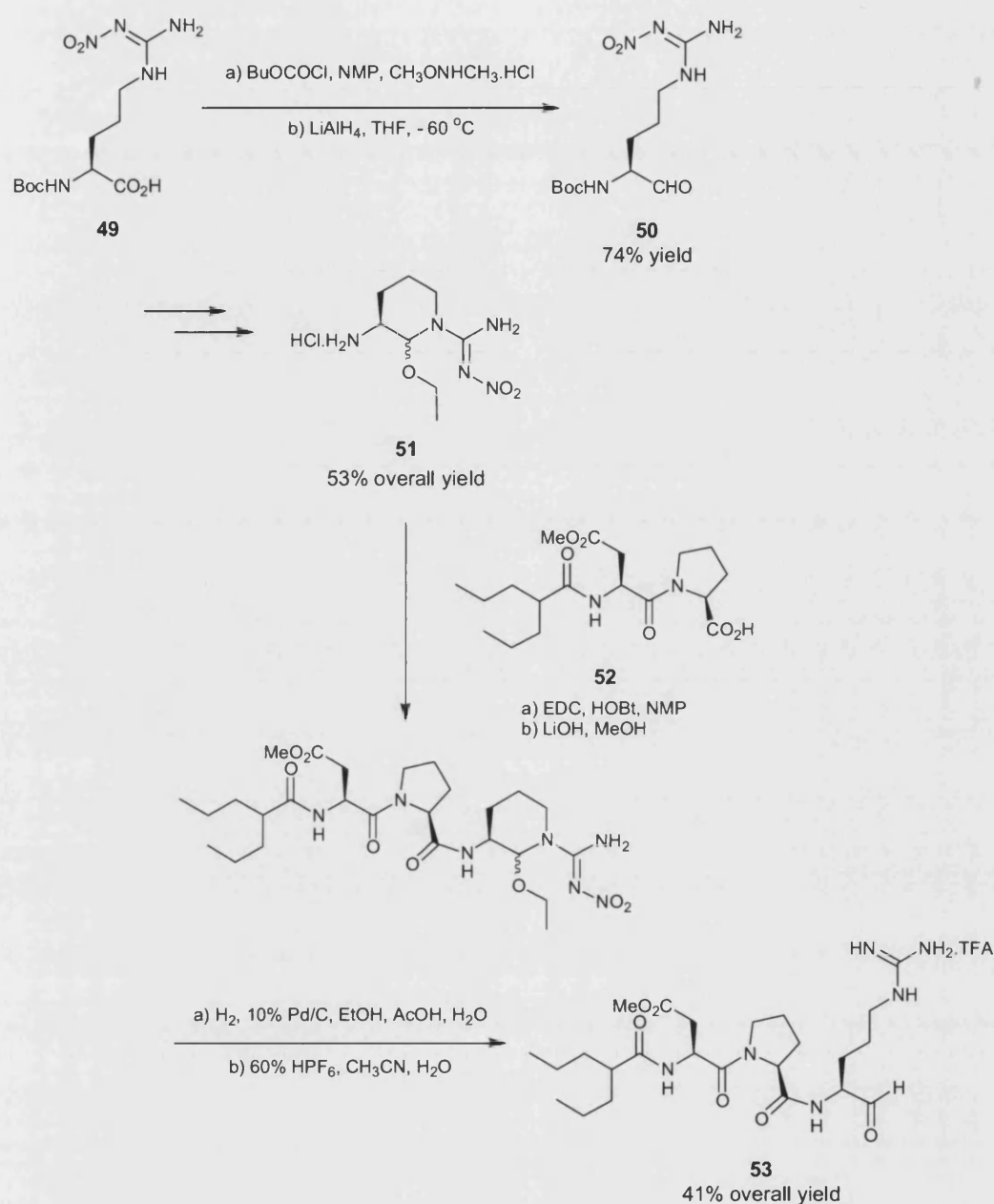
Scheme 26. Selective asymmetric dihydroxylation for the synthesis of dihydroxyaldehyde **46**

Aldehydes can also be synthesised by hydride reduction of the corresponding ester, nitrile or amide. In a similar way to oxidations, care must be taken not to over reduce the resultant aldehyde to its parent alcohol. A recent paper from the Pattenden group uses a hydride reduction to form the key aldehyde **48** in their synthesis of (\pm)-Salinosporamide A (see Scheme 27).^[26] Reduction of the malonate derivative **47** with “Super-hydride” (lithium triethylborohydride) was regioselective and proceeded in good yield with no racemisation. The regioselectivity was rationalised on steric grounds, with the bulky O-TMS group preventing hydride delivery to the *syn*-orientated ester functionality. It was also suggested that the same O-TMS group exerts an inductive electronic effect to activate the corresponding *anti*-orientated ester due to their antiperiplanar relationship.



Scheme 27. Reductive synthesis of key aldehyde **48** in the synthesis of salinosporamide A

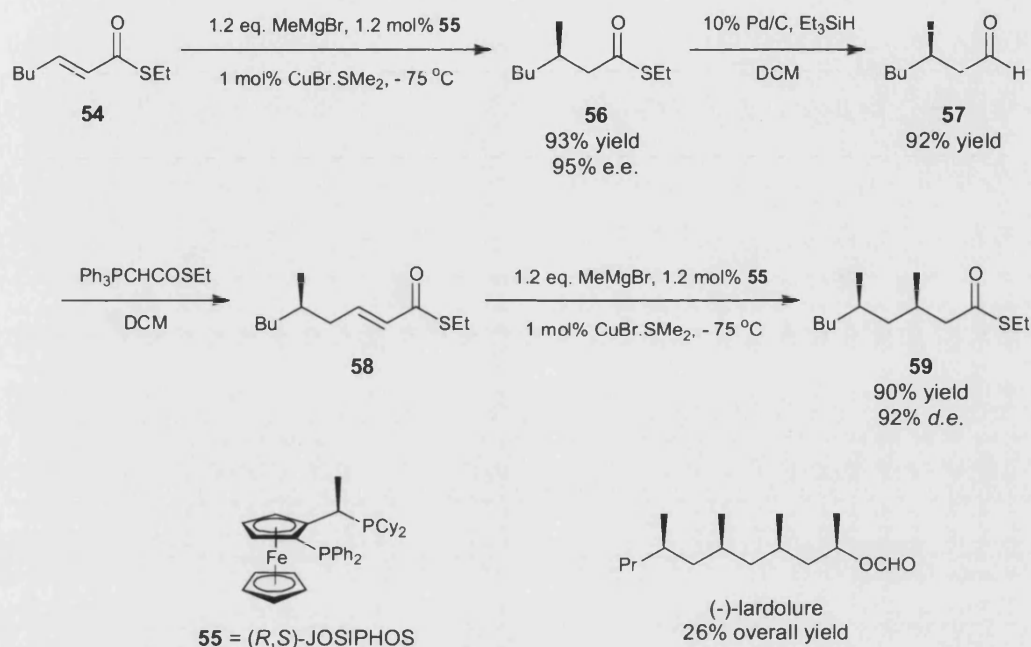
Tamura *et al.* have described the synthesis of a number of peptidyl arginals such as **53**, which are important synthetic targets as they exhibit activity as therapeutic agents for thrombotic vascular disease.^[27] *N*-Boc-nitro-L-arginal **50** is synthesised from the corresponding L-arginine **49** via its Weinreb amide (see Scheme 28). This aldehyde was then converted to the key intermediate **51** which was coupled to fragment **52** followed by hydrogenation and selective hydrolysis to afford peptidyl arginal **53** in a large scale synthesis.



Scheme 28. Synthesis of peptidyl arginal **53**

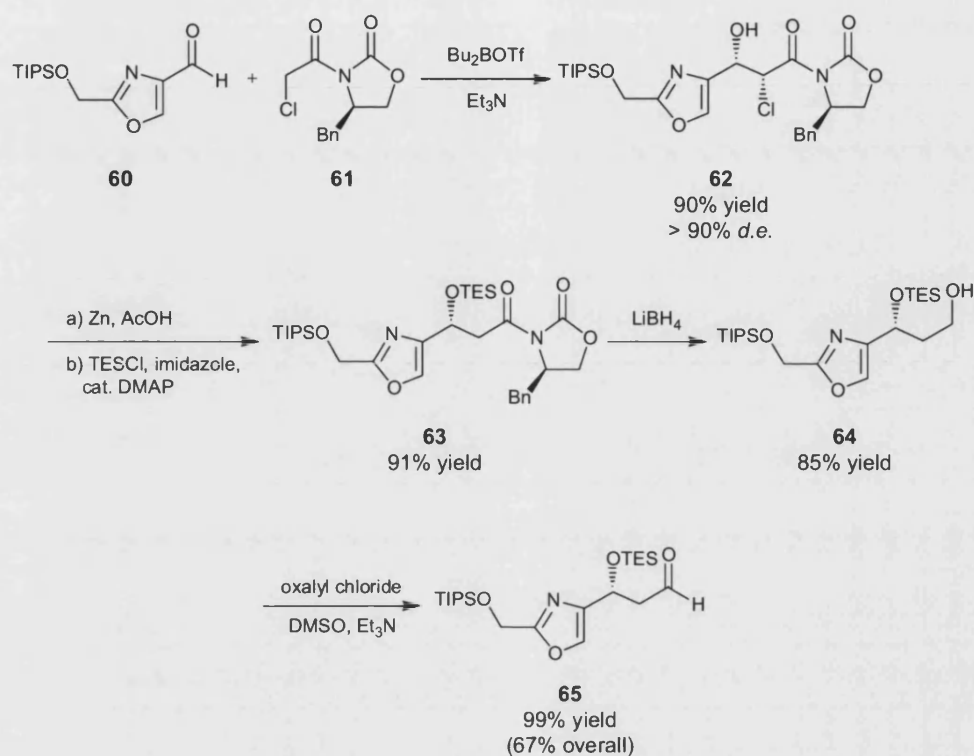
An additional reductive method for the synthesis of chiral aldehydes involves the reduction of thioesters. For example, Feringa *et al.* have described the asymmetric conjugate addition of Grignard reagents to α,β -unsaturated thioesters such as **54** in good yield and enantiomeric excess (up to 96% *e.e.*) using chiral ligand **55**.^[28] Subsequent reduction of thioester **56** with Pd/C afforded chiral aldehyde **57** in excellent yield and with no loss of enantiomeric excess (see Scheme 29). These aldehydes could also easily undergo a Wittig

reaction to yield α,β -unsaturated aldehyde **58** and by an iterative process thioester **59** could be synthesised in good yield and with good diastereoselectivity. This protocol has been exploited for the synthesis of natural product (-)-lardolure.



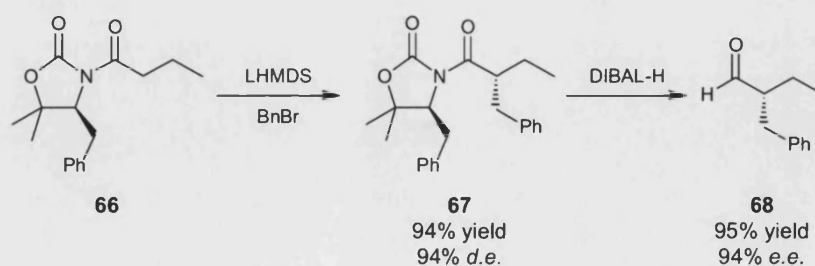
Scheme 29. Asymmetric addition of Grignard reagents to thioesters and subsequent reduction to afford chiral aldehydes

Another common method used to synthesise chiral aldehydes involves chiral auxiliaries. For example, in 2000 Evans *et al.* reported the use of their oxazolidin-2-one auxiliary to synthesise aldehyde **65** which was a key component in the synthesis of phorboxazole B.^[29] An aldol reaction between aldehyde **60** and the acylated Evans' auxiliary **61** gave β -hydroxy-*N*-acyl oxazolidin-2-one **62** in good yield with high diastereocontrol. Subsequent removal of the chloro functionality and protection of the free alcohol gave **63** in good yield. The desired chiral aldehyde **65** was obtained by reductive cleavage of the auxiliary with lithium borohydride to give alcohol **64**, followed by Swern oxidation to aldehyde **65** in 67% overall yield (see Scheme 30).



Scheme 30. Synthesis of key aldehyde **65** in the synthesis of phorboxazole B using Evans' auxiliary methodology

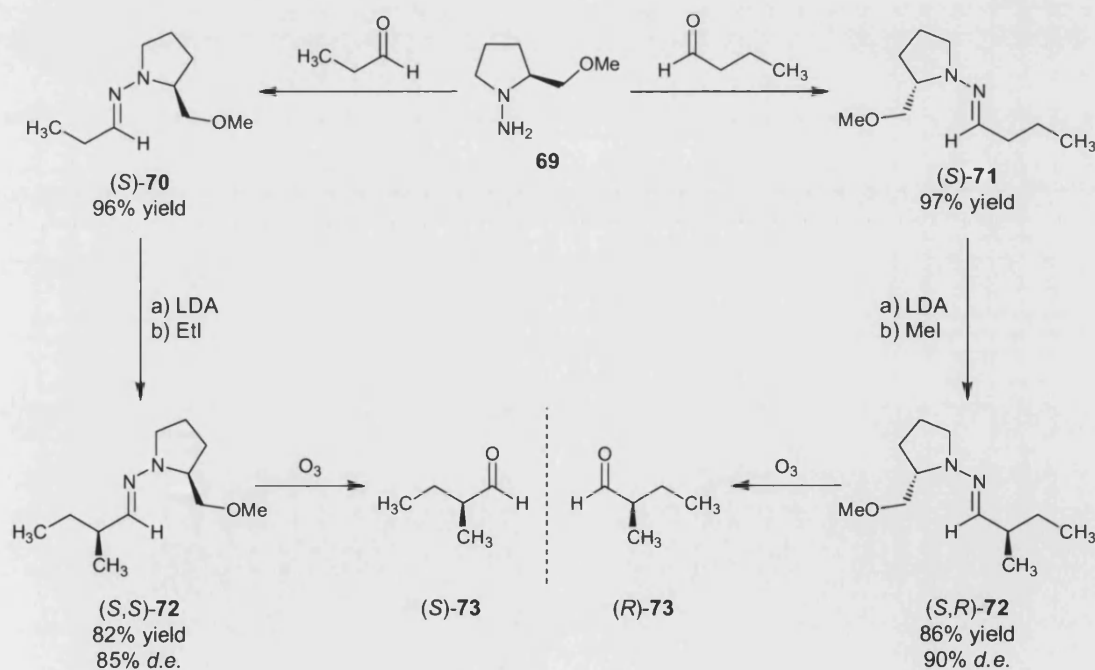
Modification of the Evans auxiliary to give the *gem*-dimethyl Superquat analogue allows for direct conversion of the auxiliary adduct to the chiral aldehyde.^[30] For example, the enolate of *N*-acylated Superquat auxiliary **66** can be alkylated with benzyl bromide to give *N*- α -benzyl-butryl oxazolidin-2-one **67** in good yield and diastereoselectivity. Subsequent treatment with DIBAL-H affords the chiral aldehyde **68** directly in good yield with no racemisation of the new chiral centre (see Scheme 31).



Scheme 31. Synthesis of chiral aldehydes by reductive cleavage of alkylated Superquat auxiliaries

Direct reductive cleavage of chiral auxiliaries with DIBAL-H to yield chiral aldehydes has also been demonstrated for L-valinol and L-phenylalaninol derived 2-phenylamino-2-oxazoline auxiliaries,^[31] a benzopyrano-isoxazolidine auxiliary^[32] and a sultam auxiliary,^[33] whilst lithium triethoxyaluminium hydride has been used for the reduction of a pseudoephedrine derived auxiliary.^[34]

One of the most widely used strategies for the synthesis of chiral aldehydes is the use of hydrazone methodology, which has already been comprehensively reviewed.^[35] For example the SAMP auxiliary **69**, first developed by Enders *et al.* in 1976,^[36] can react with prochiral aldehydes to yield hydrazone **70** and **71** in excellent yield. Subsequent deprotonation with LDA followed by alkylation with organohalides yields chiral hydrazones **72** in almost quantitative yield with good diastereoselectivity.^[35] Oxidative cleavage of the chiral hydrazone **73** with ozone yields aldehyde **XX** in good yield and enantiomeric excess. A useful feature of this methodology is that both enantiomers of aldehyde can easily be synthesised using a single enantiomer of auxiliary depending on the sequence of reactions, as shown in Scheme 32.



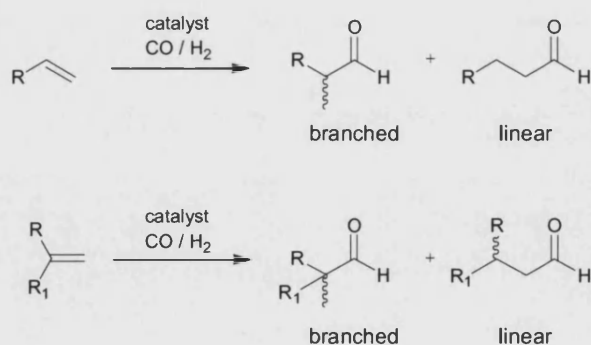
Scheme 32. Use of SAMP **69** auxiliary in hydrazone based synthesis of chiral aldehydes^[35]

The use of hydrazones can also be successfully applied using heteroatom electrophiles which can lead to the synthesis of benzyl-protected α -hydroxyaldehydes,^[37] α -thiolated aldehydes,^[38] α -silylated aldehydes^[39] and α -phosphinylaldehydes^[40] in good yields and enantiomeric excesses. In addition to alkylation reactions, aldehyde derived chiral hydrazones can take part in aldol reactions, Michael additions and rearrangements to form chiral aldehyde products.^[35]

These strategies depend on manipulation of the oxidation state or substitution pattern of a chiral substrate which obviously adds steps to the synthetic procedure. Therefore, the remaining examples in this review will concentrate on asymmetric methods that directly synthesise chiral aldehydes without the need for either oxidation or reduction to generate the aldehyde functionality.

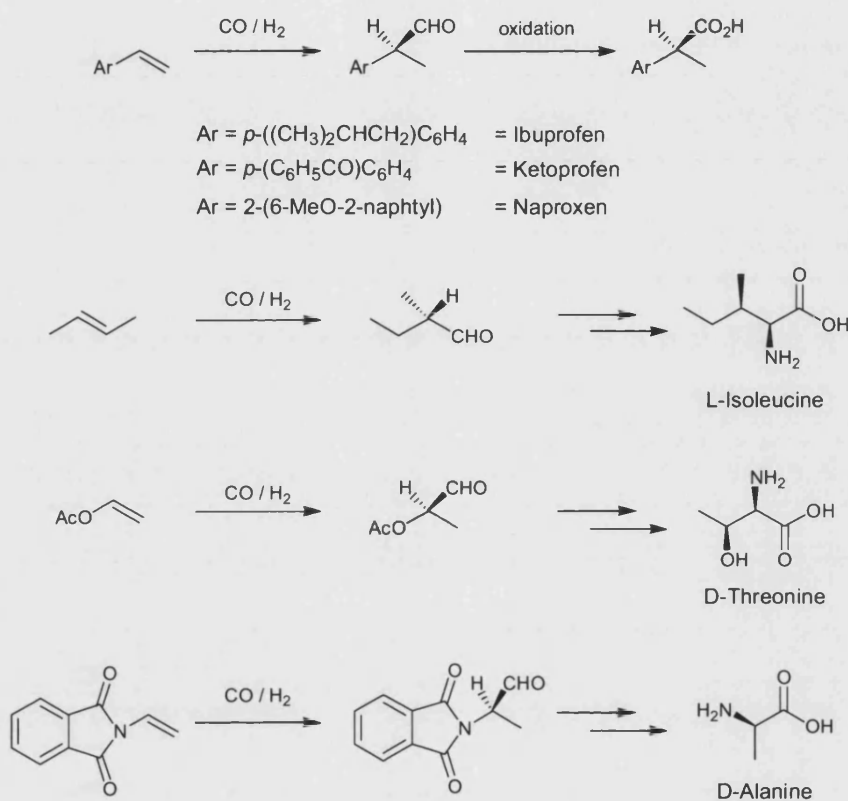
1.3.3 Asymmetric hydroformylation

Discovered in 1938 by Roelen,^[41] hydroformylation is an atom efficient process for the conversion of an alkene to an aldehyde. The challenge in asymmetric hydroformylation is not only control of enantioselectivity but also of chemoselectivity (hydroformylation vs. hydrogenation) and regioselectivity (branched vs. linear aldehyde).^[42] For mono-substituted alkenes formation of the linear aldehyde does not result in a stereogenic centre, whereas for more highly substituted alkenes enantioselectivity can arise by formation of the branched or linear product (see Scheme 33).



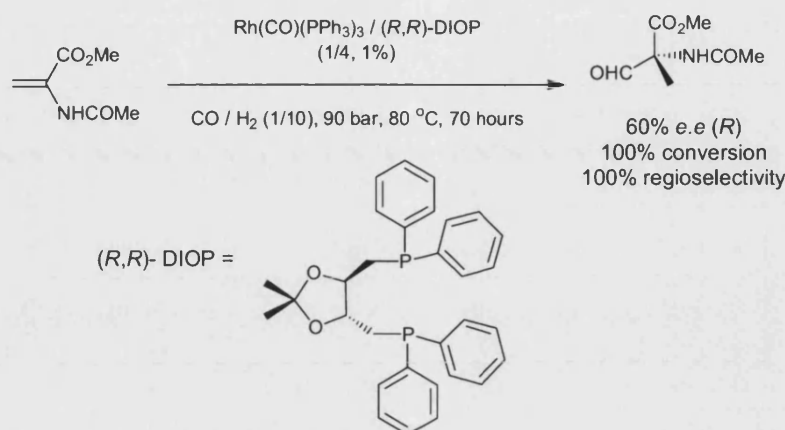
Scheme 33. Possible products arising from hydroformylation

Asymmetric hydroformylation is an important tool in the synthesis of nonsteroidal anti-inflammatory agents based on the preparation of functionalised 2-arylpropanoic acids, as well as the synthesis of optically active α -amino acids (see Scheme 34).^[42]



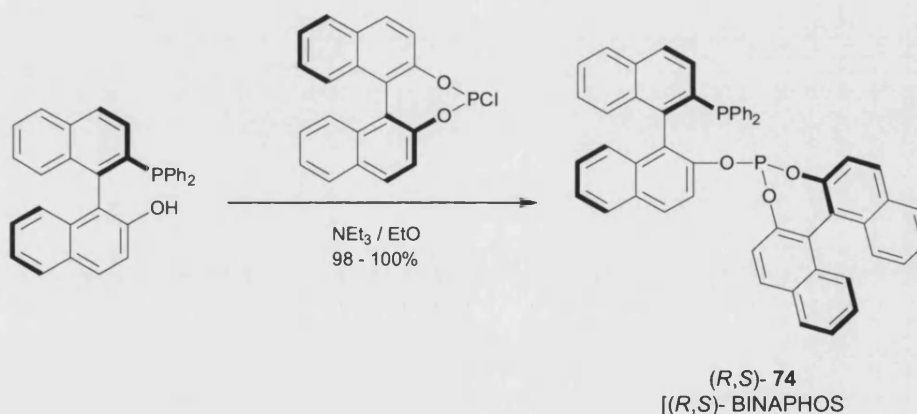
Scheme 34. Chiral drug intermediates and amino acids that have been synthesised by asymmetric hydroformylation^[42]

Preliminary work into catalyst systems capable of affecting asymmetric hydroformylation were carried out using rhodium and platinum systems containing phosphine ligands. Prior to 1992, rhodium catalysis achieved only moderate enantioselectivities, whilst competing hydrogenation and regioselectivity issues were often a problem with platinum systems.^[43] The best example for a rhodium(I) catalyst was 60% enantiomeric excess for the hydroformylation of methyl α -acetamidoacrylate catalysed by DIOP-Rh(I) complexes (see Scheme 35).^[44]



Scheme 35. Asymmetric hydroformylation of methyl α -acetamidoacrylate catalysed by Rh(I)-DIOP

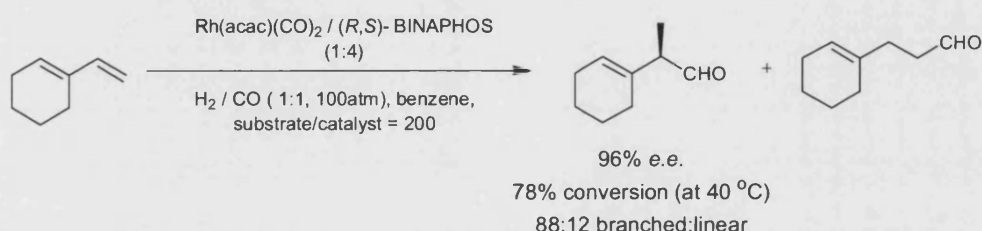
In 1993 Takaya *et al.* reported the development of the BINAPHOS ligand **74**, a chiral phosphinephosphite ligand which affords a highly efficient catalyst for asymmetric hydroformylation when complexed to rhodium (I) (see Scheme 36).^[45]



Scheme 36. Synthesis of (*R,S*)-BINAPHOS ligand **74**

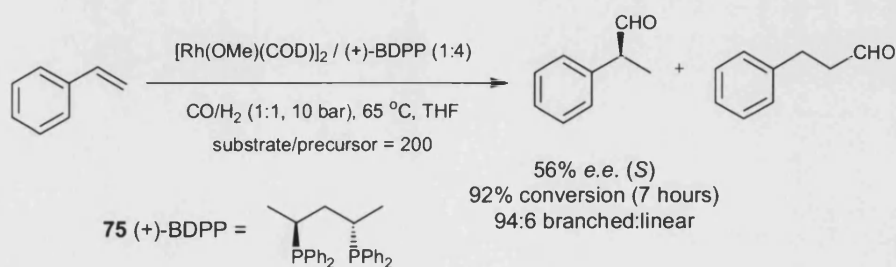
The rhodium complex was used for the asymmetric hydroformylation of a range of arylethenes and functionalised olefins including vinyl acetate and *N*-vinylphthalimide in good yields (> 90%), and with good enantioselectivity (75 – 94% e.e.) and regioselectivity. The best results were obtained for the hydroformylation of hept-1-ene which proceeded in greater than 99% conversion, 94% enantiomeric excess and a branched to linear ratio of 88:12.

The group further extended the use of their catalyst system to allow for the asymmetric hydroformylation of 1,2-disubstituted olefins in excellent regioselectivity (up to 98:2) and enantioselectivity (up to 97%),^[46] and to the asymmetric hydroformylation of conjugated dienes, an area where previous efforts had been disappointing (see Scheme 37).^[47] In this case hydroformylation was highly selective for the terminal alkene, and ratios of branched to linear products were high (up to 95:5). However, very high pressures of hydrogen and carbon monoxide (100 atm.) and long reaction times (up to 108 hours) were required to achieve these results. This protocol has also been extended to allow highly regio- and enantioselective hydroformylation without organic solvents,^[48] and more recently a polymer supported version of the BINAPHOS ligand has been developed which exhibits regio- and enantioselectivity comparable to the solution phase version.^[49,50]



Scheme 37. Rh(I)-BINAPHOS catalysed asymmetric hydroformylation of conjugated dienes

Having studied the structures of the most common phosphine ligands used for asymmetric hydroformylation, Masdeu-Bultó *et al.* concluded that simple diphosphines such as BDPP **75** should be effective at influencing enantioselectivity in the hydroformylation reaction.^[51] They reported the use of a $[\text{Rh}(\mu\text{-OMe})(\text{COD})]_2 / (+)\text{-BDPP}$ catalyst precursor system to affect the hydroformylation of styrene in good yield, regioselectivity and reasonable enantioselectivity (see Scheme 38). Although the enantioselectivity was disappointing in comparison with BINAPHOS, much milder conditions and shorter reaction times were used in this reaction, combined with the use of a much more easily prepared ligand.



Scheme 38. Asymmetric hydroformylation of styrene with (+)-BDPP **75**

Subsequent ligands developed for the rhodium catalysed asymmetric hydroformylation reaction include BINAP,^[52] NAPHOS,^[53] BIPHLOPHOS,^[54] and the ribafuranose derivative **76** (see Figure 1).^[55] However in all these cases no major improvements were observed with the best enantioselectivities obtained being around 60%, and whilst regioselectivity was often excellent, conversion rates were often poor.

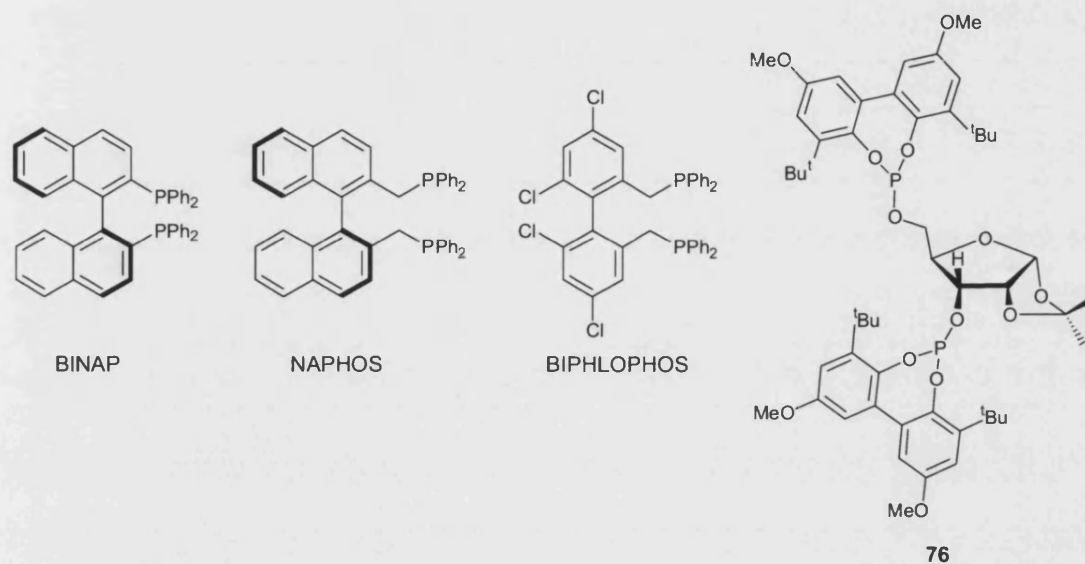
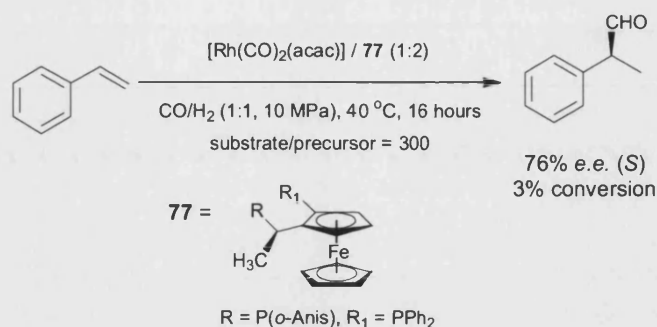


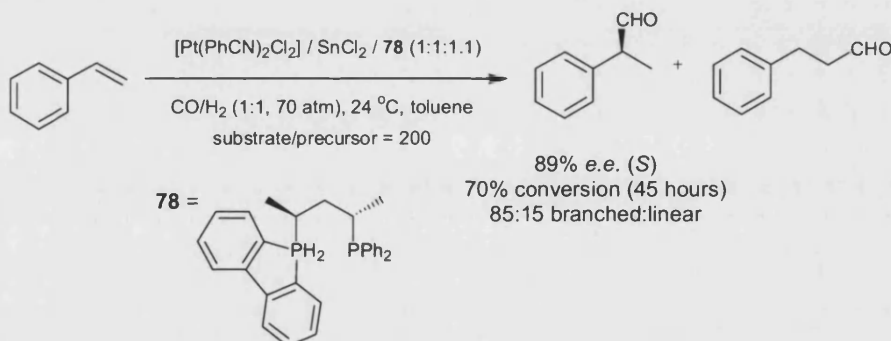
Figure 1. Examples of ligands developed for the rhodium catalysed asymmetric hydroformylation reaction

Herrmann *et al.* describe the use of a variety of chiral ferrocenylethyl diphosphines **77** with rhodium(I) precursors for the asymmetric hydroformylation of styrene.^[56] The presence of an *ortho*-anisyl substituent on phosphorus allowed enantioselectivities up to 76% *e.e.*, with good levels of regiocontrol (see Scheme 39). However conversions in these reactions were once again very poor, and any attempts to improve yields were to the detriment of enantioselectivity.



Scheme 39. Chiral ferrocenylethyl diphosphines as ligands for the rhodium catalysed asymmetric hydroformylation of styrene

Improvements to the platinum catalysed asymmetric hydroformylation have also been described. Hegedis *et al.* reported the use of a novel chiral phosphine-phosphole ligand **78** which can be used with a platinum precursor to affect the hydroformylation of styrene with excellent levels of regio- and enantiocontrol (see Scheme 40).^[57] Furthermore, high enantioselectivities could be achieved using relatively short reaction times, under lower pressures of syngas and at ambient temperatures.



Scheme 40. Novel phosphine-phosphole ligand for the platinum catalysed asymmetric hydroformylation of styrene

More recently several new ligands have been developed for the asymmetric hydroformylation reaction.^[58,59] These include (S,S)-kelliphite which affords enantioselectivities in up to 88% e.e. with excellent regioselectivity for the hydroformylation of allyl cyanide and vinyl acetate,^[60] (2R,4R)-chiraphite which displays enantioselectivities up to 90% e.e. for hydroformylation of styrene,^[61] (S,S)-ESPPOS

which exhibits high enantioselectivities for the hydroformylation of vinyl acetate^[62] and (*R,R*)-Ph-BPE and the bis-3,4-diazaphospholone **79** which show high catalyst activity and excellent regio- and stereocontrol (up to 96%) for the hydroformylation of styrene, allyl cyanide and vinyl acetate (see Figure 2).^[63,64]

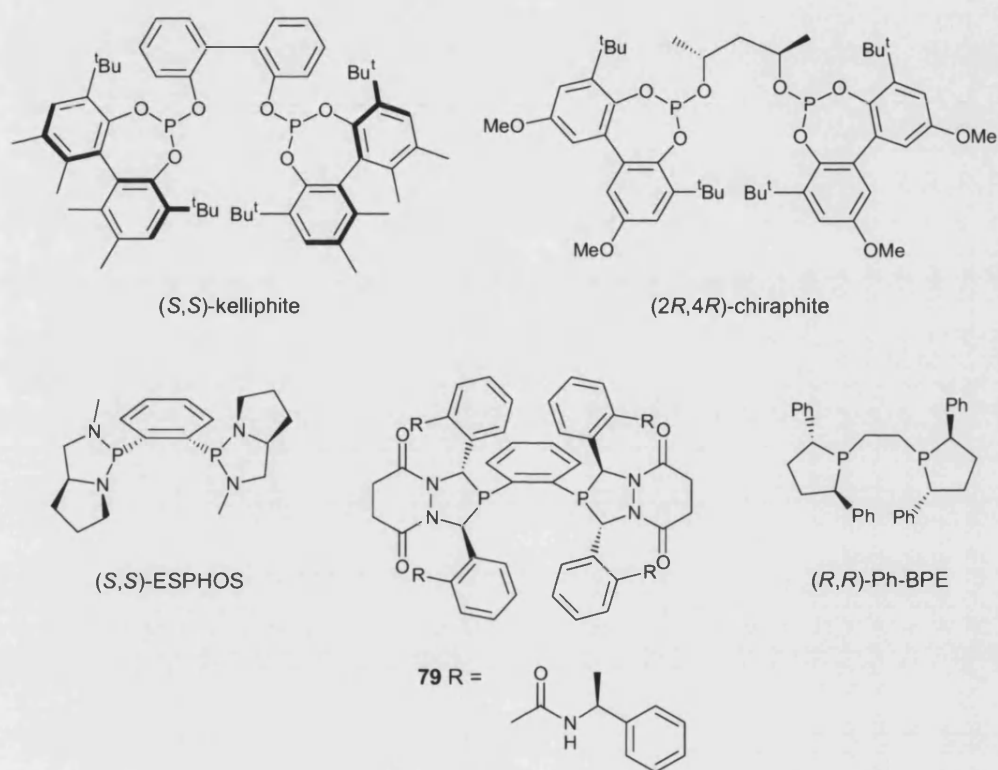
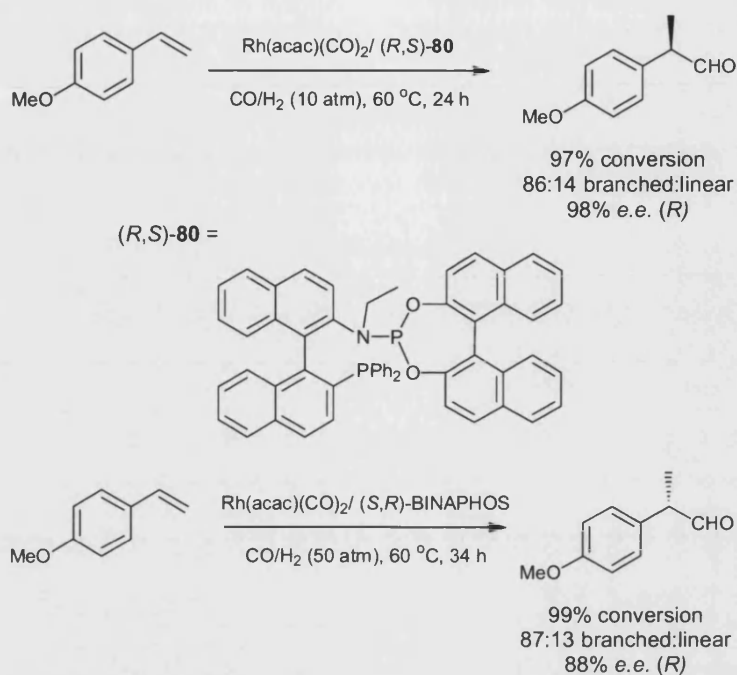


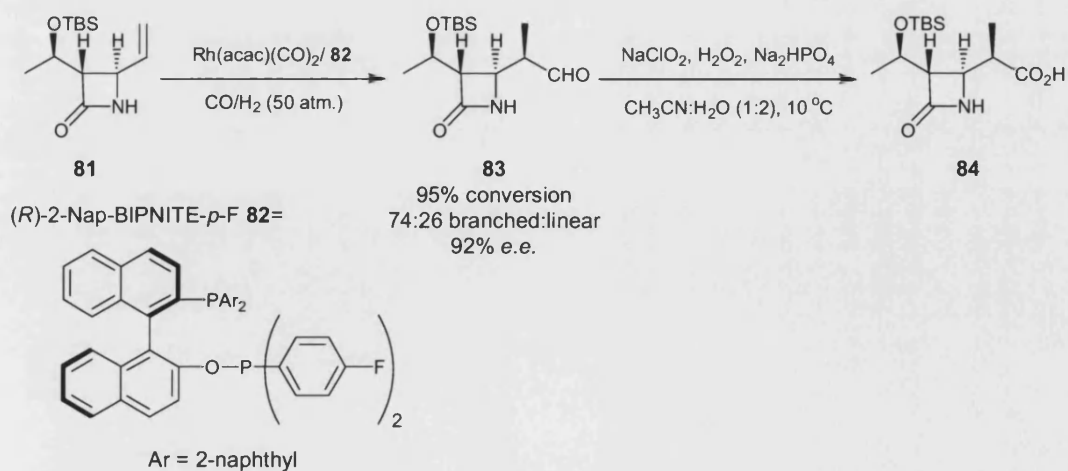
Figure 2. Recent examples of chiral ligands used for asymmetric hydroformylation

In 2006, Zhang *et al.* reported that a small modification to the (*R,S*)-BINAPHOS ligand allowed for very high enantioselectivities (up to 99% *e.e.*) for the asymmetric rhodium catalysed hydroformylation of styrene derivatives and vinyl acetate.^[65] For example the hydroformylation of *para*-methoxy styrene with ligand **80** was achieved with excellent 98% enantiomeric excess compared to the 88% *e.e.* reported for BINAPHOS and with much lower pressures of syngas and shorter reaction times (see Scheme 41).



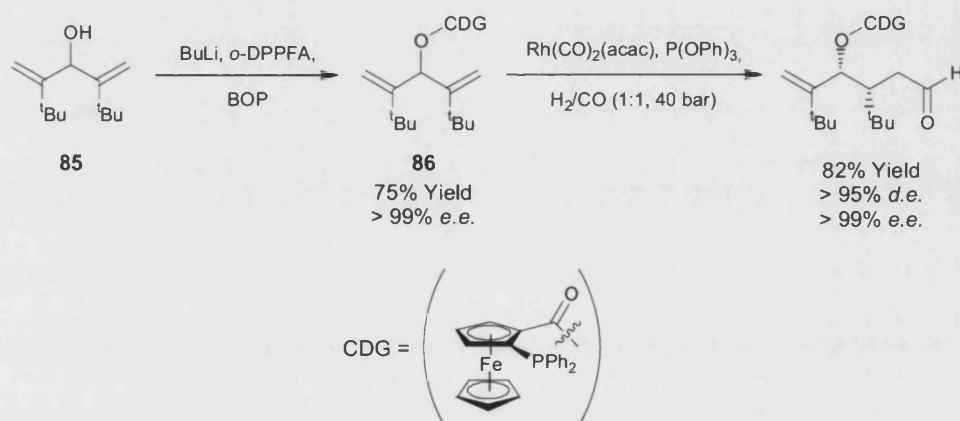
Scheme 41. Rhodium catalysed hydroformylation of *p*-methoxy styrene using ligand **80**

Nozaki *et al.* have exploited the rhodium catalysed asymmetric hydroformylation reaction for the synthesis of β -lactam **84** which is a key intermediate in the synthesis of 1 β -methylcarbapenem antibiotics.^[66] Chiral β -lactam aldehyde **83** was synthesised by asymmetric hydroformylation from 4-vinyl- β -lactam **81** using the 2-Nap-BIPNITE-*p*-F ligand **82** in good yield and enantioselectivity (see Scheme 42) Subsequent oxidation afforded the key compound **84** with no epimerization.



Scheme 42. Synthesis of β -lactam **84** by asymmetric hydroformylation

Although the control of enantioselectivity using these types of ligands has provided a significant advancement in the area of asymmetric hydroformylation, the range of substrates that can be used in these reactions is still relatively limited. One method that may overcome this is the use of a substrate-bound catalyst directing group (CDG) which allows for diastereoselective hydroformylation of substrates. Breit *et al.* have developed this strategy for the desymmetrising hydroformylation of prochiral dialkenylcarbinols **85** and diallylcarbinols using a planar –chiral catalyst-directing group.^[67-69] Desymmetrisation of these compounds is achieved by coordination of the hydroxyl group of the carbinol substrate to form an *ortho*-diphenylphosphanyl ferrocene adduct **86**. This species then directs the hydroformylation reaction to one of the enantiotopic alkenes with excellent enantio- and diastereoselectivity (see Scheme 43). Removal of the directing group is achieved by saponification of the ester functionality with ethanolic potassium hydroxide solution, which requires prior protection of the aldehyde as its dimethyl acetal.

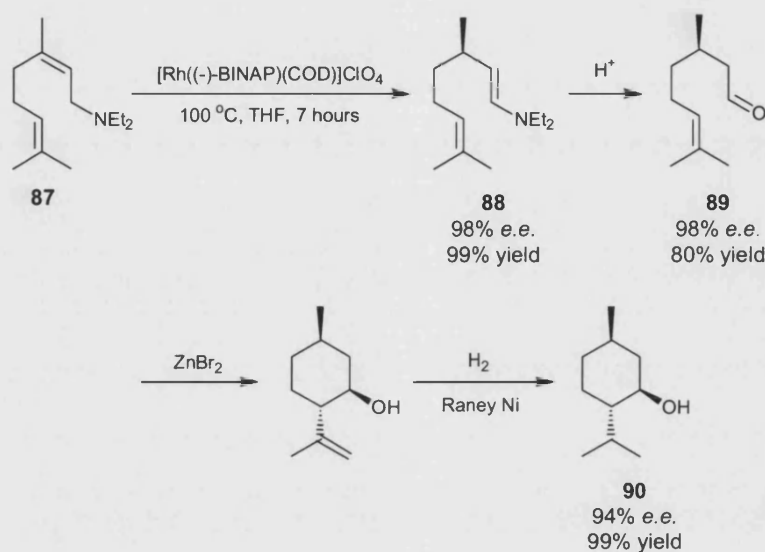


Scheme 43. Desymmetrising hydroformylation using a planar-chiral catalyst-directing group

1.3.4 Catalytic asymmetric isomerisation

The catalytic asymmetric isomerisation of prochiral allylic amines has been shown to be an effective method for the synthesis of chiral aldehydes via chiral enamines. In 1978 Otsuka *et al.* reported the use of a chiral cobalt complex catalyst to affect the asymmetric isomerisation of geranyl- and nerylamine derivatives, however the enantioselectivity of the cobalt catalysts investigated was too low to be synthetically useful (approximately 30% e.e.).^[70] Later the development of a rhodium (I) BINAP complex catalyst was found

to be successful for the asymmetric isomerisation of allylic amines,^[71] which subsequently led to its development for the industrial scale preparation of (-)-menthol and other related terpenes from geranylamine.^[72] The prochiral allylic amine **87** is isomerised with [Rh((-)-BINAP)(COD)]ClO₄ to give chiral enamine **88** in excellent yield and enantioselectivity. Subsequent hydrolysis with dilute sulfuric acid affords (+)-citronellal **89** which can then be stereoselectively cyclised and reduced to *l*-menthol **90** in good yield and enantioselectivity (see Scheme 44).

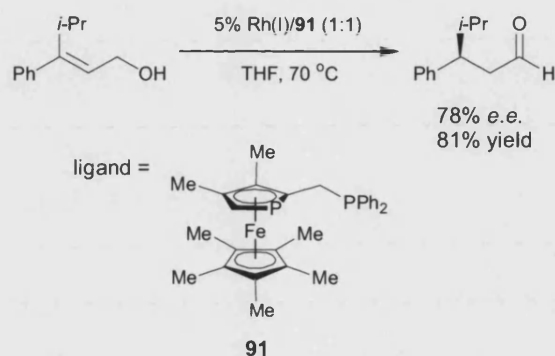


Scheme 44. Catalytic asymmetric isomerisation of allylic amines

The reaction is thought to proceed by a 1,3-hydride shift involving a η -allyl intermediate.^[73] Interestingly, the resulting chiral enamine was found to always possess (*E*)-alkene geometry regardless of the geometry of the prochiral allylamine. Also there are no chemoselectivity issues in isomerisation of allylic amines such as **87** which contain two different types of alkene functionality. The complex is stable, maintaining high levels of stereocontrol through several catalyst turnovers.

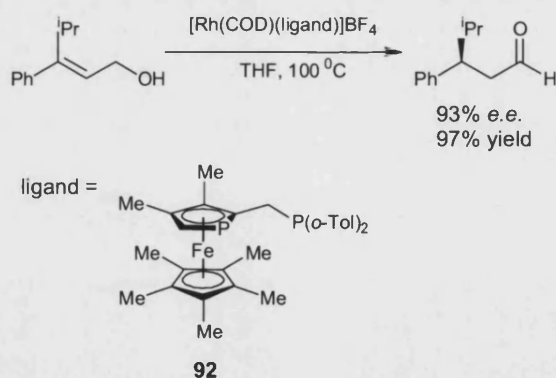
Although the isomerisation of allylic amines has proved to be a synthetically useful process, isomerisation of allylic alcohols would have the advantage that it is a completely atom economic process, however this area has been much less studied. In 2000 Fu *et al.* reported the use of a planar-chiral phosphaferrrocene **91** to affect the asymmetric isomerisation of (*Z*)-allylic alcohols with good enantioselectivity (64 – 86% e.e.) and

reasonable yield (55 – 91%) (see Scheme 45).^[74] This was a considerable breakthrough as previously the highest enantioselectivity achieved was 53% *e.e.* for the asymmetric isomerisation of (*E*)-3-phenyl-but-2-en-1-ol with a rhodium(I) BINAP catalyst in 47% yield.^[74,75]



Scheme 45. Asymmetric isomerisation of allylic alcohols with planar-chiral phosphaferrrocene ligand **91**

This procedure was further developed in 2001 by modification of the phosphine substituent to an *ortho*-tolyl group in place of the phenyl groups. This allowed access to a much more robust ligand **92**, which was not only more air stable but also significantly improved the scope, enantioselectivity (57 – 93% *e.e.*) and yield (60 – 98%) of these reactions (see Scheme 46).^[76]

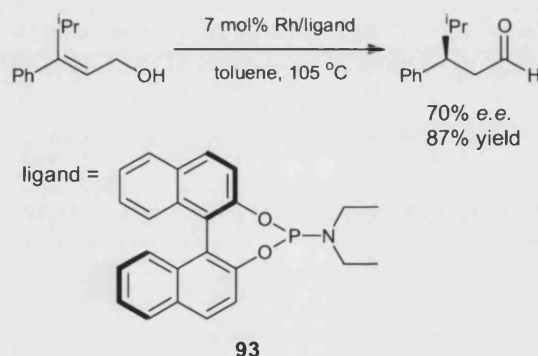


Scheme 46. Asymmetric isomerisation of allylic alcohol with modified planar-chiral phosphaferrrocene ligand **92**

Interestingly it was discovered that use of the air stable, crystalline [Rh(COD)(**92**)]BF₄ complex was found to give higher enantioselectivity than the previously used [Rh(**92**)]BF₄

which was made via hydrogenation of $[\text{Rh}(\text{COD})(\mathbf{92})]\text{BF}_4$ as a precatalyst. This simplifies the reaction procedure and also allows for the catalyst to be easily recyclable without significant loss of enantioselectivity or yield. It was also found that the highest enantioselectivities were obtained with (*E*)-allylic alcohols in contrast to previous reports. Mechanistic studies have shown that this reaction is likely to proceed via an intramolecular 1,3-migration pathway analogous to the pathway found for asymmetric isomerisation of allylic amines.

Recently Crévisy *et al.* reported the first use of a rhodium phosphoramidite complex to catalyse the enantioselective isomerisation of allylic alcohols. This uses ligand **93** to effect asymmetric isomerisations of a range of allylic alcohols in high yield (84 – 89%) with moderate to good enantioselectivities (38 – 70%) as shown in Scheme 47.^[77] In concordance with Fu's work it was found that isomerisations of (*E*)-allylic alcohols proceeded with higher stereoselectivities than those starting from (*Z*)-allylic alcohols, and that a 1,3-hydride shift is involved in this reaction.

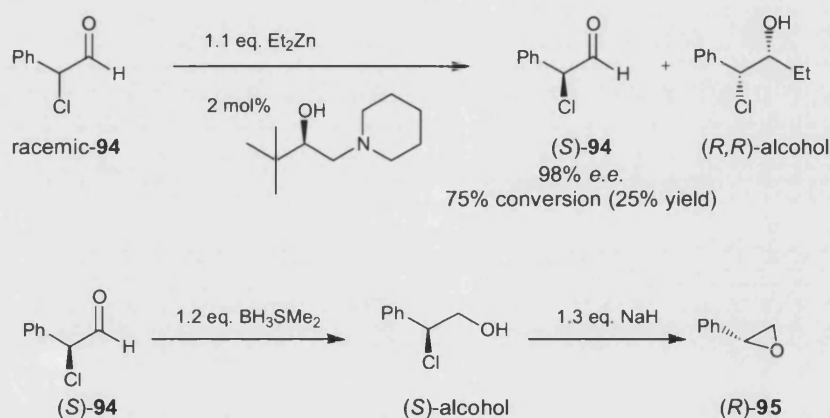


Scheme 47. Asymmetric isomerisation of allylic alcohols catalysed by a rhodium(I) phosphoramidite complex

Although the enantioselectivities achieved in this reaction are not as high as those reported by Fu, it serves to highlight that further research should be directed towards development of novel, easily accessible ligands to affect these transformations.

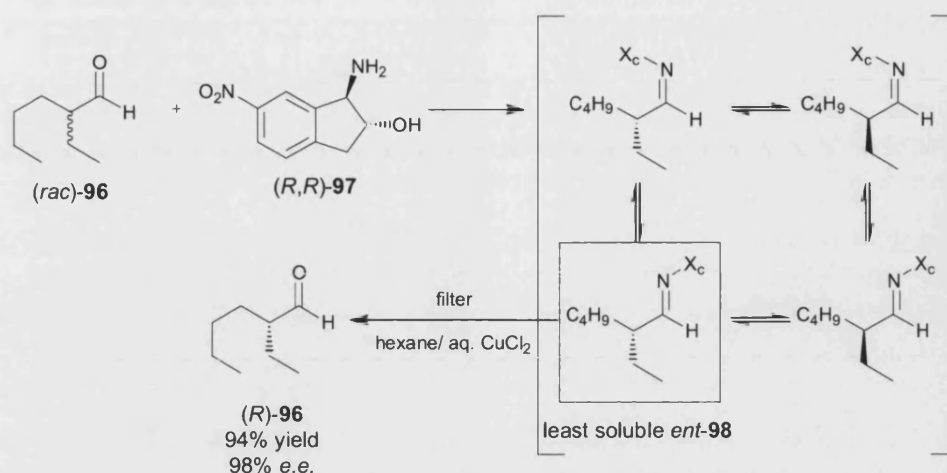
1.3.5 Kinetic resolution

Kinetic resolution of racemic compounds is a useful strategy for the synthesis of chiral molecules.^[78] In 1989 Oguni *et al.* reported the use of diethyl zinc in the presence of small amounts of chiral β -amino alcohols for the kinetic resolution of racemic aldehydes by enantioselective alkylation.^[79] It was found that when the (*R*)-enantiomer of the β -amino alcohol ligand was used, the (*R*)-enantiomer of the aldehyde reacted faster affording the (*R*)-alcohol and the enantiomerically enriched (*S*)-aldehyde. This reaction has been adapted to a range of aldehydes using various β -amino alcohols with moderate success and has been exploited for the synthesis of styrene oxide **95** from resolved α -chloro(phenyl)acetaldehyde **94** (see Scheme 48).^[80]



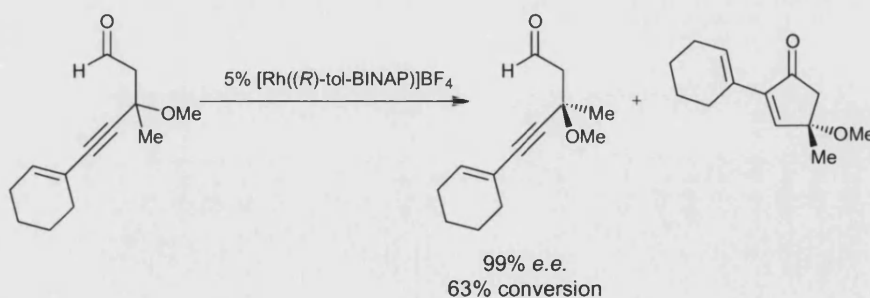
Scheme 48. Kinetic resolution of aldehydes by enantioselective alkylation for the synthesis of styrene oxide

More recently Košmrlj *et al.* have reported the crystallization-induced dynamic resolution of a number racemic ketones and aldehydes.^[81] For example, racemic aldehyde **96** was reacted with chirally pure amine **97** to afford four rapidly equilibrating diastereomers of aldimine **98** in quantitative yield. Subsequent stirring and concentration resulted in continuous precipitation of the most crystalline aldimine which was then hydrolysed to afford chiral aldehyde (*R*)-**96** in excellent enantiomeric excess and in 94% yield (see Scheme 49).



Scheme 49. Crystallisation-induced dynamic resolution of racemic aldehyde **96**

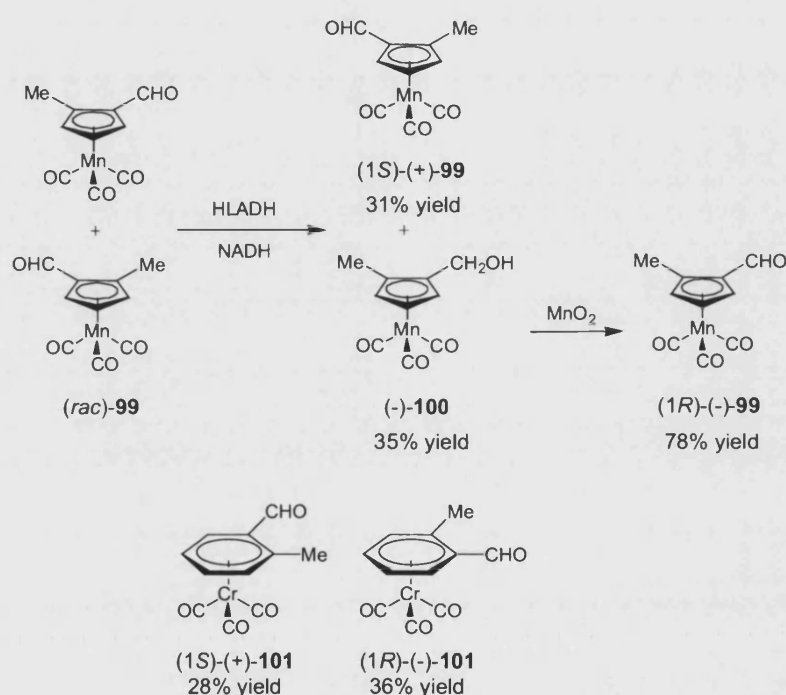
Fu *et al.* have developed a new method for the rhodium catalysed synthesis of cyclopentenones from 4-alkynals,^[82] and have exploited the asymmetric variant of this reaction to allow for the kinetic resolution of racemic alkynals as shown in Scheme 50.^[83] This reaction has been applied to a range of alkynal substrates resulting in excellent levels of enantiomeric excess in the unreacted alkynal (93 – 99% *e.e.*). For substrates with a tertiary stereocentre at the β - carbon, DUPHOS was used as a chiral ligand, whilst Tol-BINAP was used for substrates where the β - carbon was a quaternary centre. The difference in rate between the faster and slower reacting enantiomers was different enough for either the enantiomerically enriched aldehyde or the chiral cyclopentenone to be isolated in good enantiomeric excess at approximately 60% conversion.



Scheme 50. Rhodium catalysed kinetic resolution of racemic 4-alkynals

Another important resolution strategy is the use of enzymes as catalysts for stereocontrol. Yamazaki *et al.* reported the use of horse liver alcohol dehydrogenase (HLADH) for the

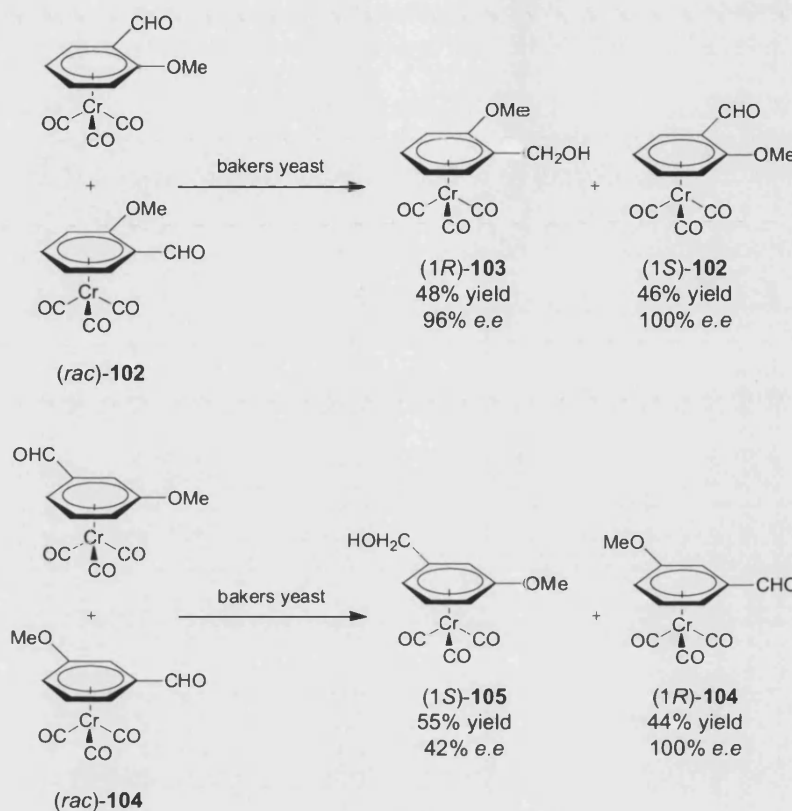
kinetic resolution of formyl-substituted derivatives of tricarbonyl(cyclopentadienyl) manganese and (benzene)tricarbonyl chromium.^[84] Racemic 1-formyl-2-methyl tricarbonyl(cyclopentadienyl) manganese **99** was reduced with HLADH and NADH to yield alcohol **100** and unreacted (*S*)-aldehyde **99**. Once separated the alcohol could be oxidised back to its enantiomerically pure (*R*)-aldehyde **99** using manganese dioxide in good yield (see Scheme 51). The same procedure was used to obtain both enantiomers of tricarbonyl(2-methylbenzaldehyde) chromium **101**, which allowed easy access to both enantiomers of the tricarbonyl complexes in 100% enantiomeric excess.



Scheme 51. HLADH mediated kinetic resolution of chiral metallocenic aldehydes

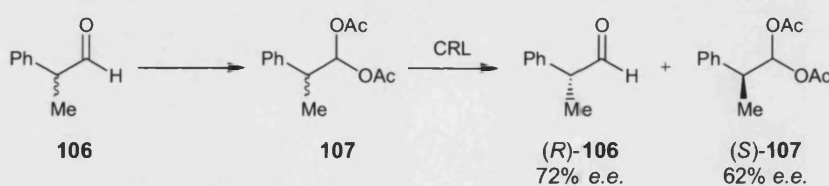
This approach has been extended by Jaouen *et al.* for the resolution of a range of other *ortho*- and *meta*-substituted tricarbonylchromium benzaldehydes using bakers yeast.^[85] *Ortho*-substituted methoxy, methyl, chloro, fluoro and trimethylsilyl benzaldehydes **102** were reduced with bakers yeast to their (1*R*)-alcohols **103** and the unchanged (1*S*)-aldehyde **102** which could be isolated with good enantioselectivity (see Scheme 52). Reduction of the *meta*-substituted methoxy and methyl benzaldehydes **104** resulted in the opposite selectivity yielding the (1*S*)-alcohol **105** and unchanged (1*R*)-aldehyde **104** under the same conditions. After isolation the compounds could be recrystallised to give chiral

aldehydes with very high enantiopurity (values quoted after recrystallisation, see Scheme 52).



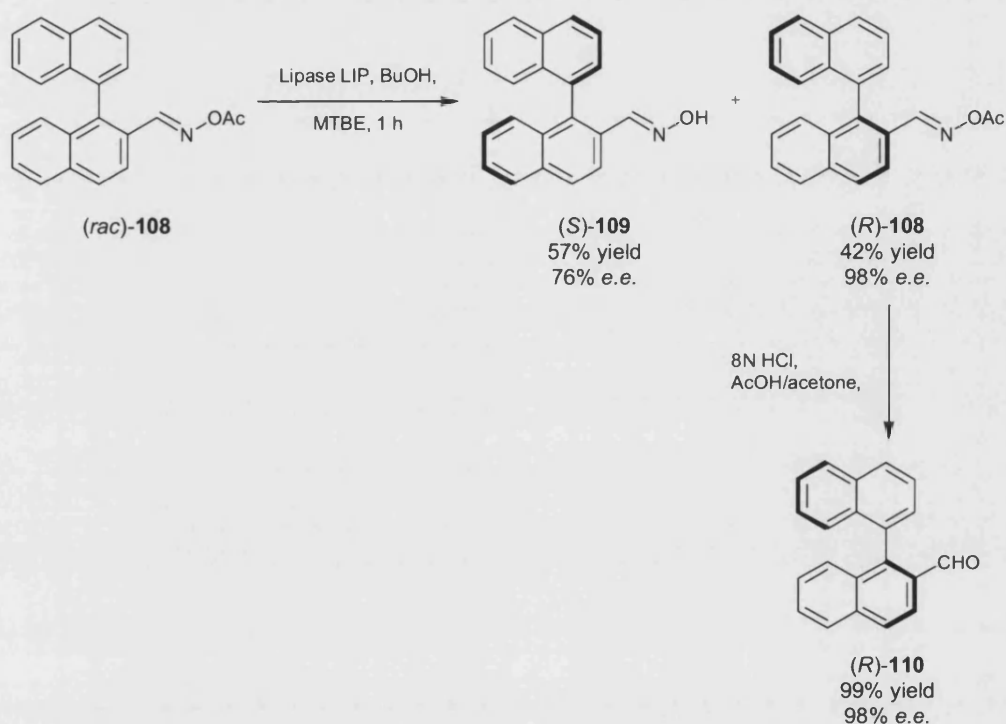
Scheme 52. Resolution of *ortho*- and *meta*-substituted tricarbonylchromium benzaldehydes by bakers yeast

Smonou *et al.* developed an enzymatic resolution of more simple aldehydes using *Candida rugosa* lipase (CRL).^[86] Racemic 2-phenyl-propanal **106** was converted to its acylal **107** and then enantioselectively hydrolysed back to a mixture of the enantiomerically enriched starting aldehyde (*R*)-**106** and unchanged acylal (*S*)-**107** by CRL (see Scheme 53). A number of different enzymes were tested for this hydrolysis reaction but it was found that CRL gave the best enantioselectivity over the shortest reaction time (70 minutes for 25% conversion).



Scheme 53. Resolution of protected 2-phenylpropanal with CRL

Aoyagi *et al.* have reported the asymmetric synthesis of 2-formyl-1,1'-binaphthyl (*R*)-**110** using the lipase catalysed kinetic resolution of acetyloxime **108**, which was easily synthesised by a Suzuki cross coupling.^[87] For example using *Pseudomonas* species LIP, kinetic resolution of acetyloxime **108** was carried out in good yield and high enantioselectivity followed by acid hydrolysis to afford (*R*)-**110** in excellent yield and without any loss of enantiomeric excess (see Scheme 54).



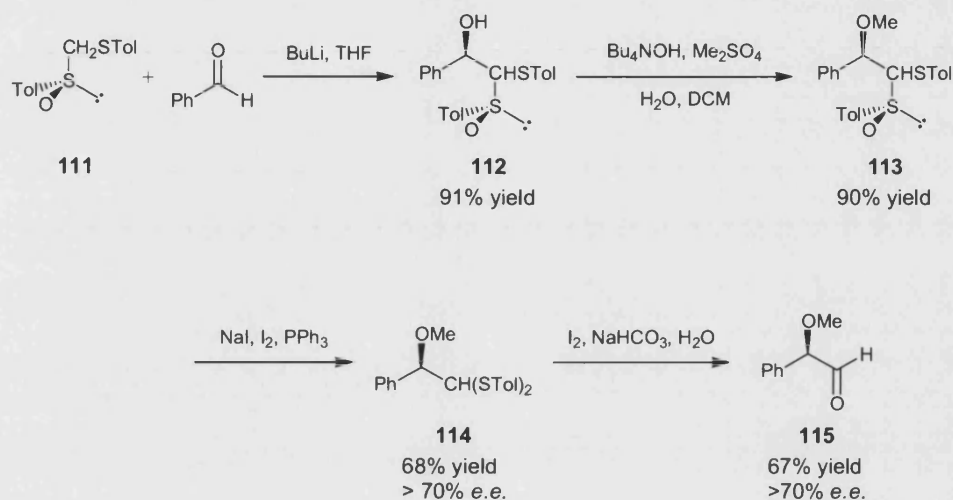
Scheme 54. Kinetic resolution of racemic oxime **108** in the synthesis of chiral aldehyde **110**

Although these types of kinetic resolution protocols can be an effective method in asymmetric synthesis, the major disadvantage is the limit to reaction yield, with even the most successful reactions producing a 50% yield of the desired chiral product.

1.3.6 Chiral masked aldehyde equivalents

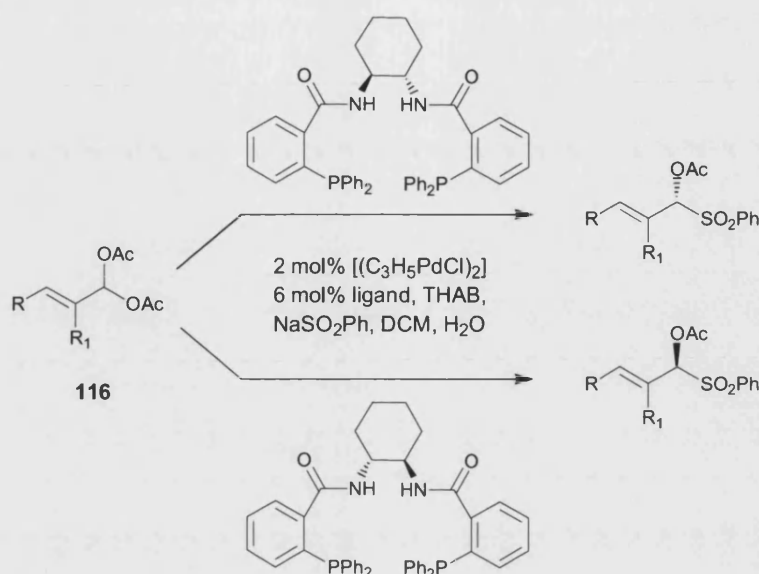
Chiral sulfur compounds can be used as aldehyde equivalents in asymmetric synthesis, allowing access to umpolung reactivity of carbonyl compounds. Scolastico *et al.* reacted the anion of sulfoxide **111**, which is a chiral formyl anion equivalent, with benzaldehyde to

give the sulfoxide adduct **112** as a mixture of diastereomers.^[88] This adduct was then *O*-methylated to overcome the instability of the hydroxyl adduct to give **113** in good yield. Subsequent reduction of the sulfoxide substituent of **113** and hydrolysis of the dithioacetal fragment of **114** affords the chiral α -methoxy aldehyde **115** in reasonable yield and greater than 70% *e.e.* (see Scheme 55).



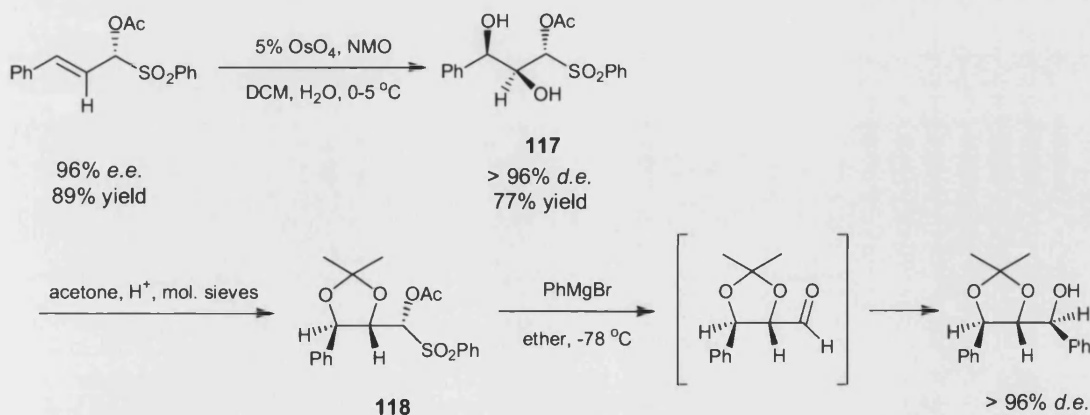
Scheme 55. Synthesis of α -methoxy aldehyde **115** using a formyl anion equivalent

Trost *et al.* developed this methodology further by using chiral α -acetoxysulfones derived from α,β -unsaturated aldehydes.^[89] Chiral α -acetoxysulfones are readily synthesised by palladium catalysed asymmetric allylic alkylation reactions of allylic gem diesters **116** in good yield (73 – 94%) and excellent enantioselectivity (> 94% *e.e.*) as shown in Scheme 56. Furthermore, either enantiomer of chiral acetoxysulfone may be easily accessed depending on the configuration of the chiral phosphine ligand used for complex formation.



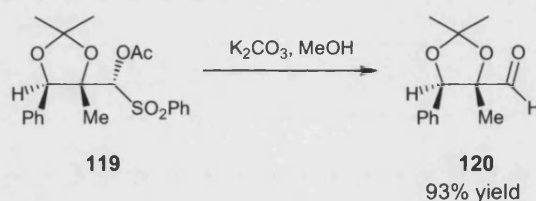
Scheme 56. Palladium catalysed asymmetric allylic alkylation for the synthesis of chiral α -acetoxysulfones

A range of these α -acetoxysulfones have been synthesised and used to direct dihydroxylation reactions with osmium tetroxide and *N*-methylmorpholine oxide to yield the corresponding diols **117** in good yield (57 – 94%) and with excellent diastereocontrol (mostly >90% *d.e.*). Since hydrolysis to the chiral aldehyde is difficult at this stage, the diol **117** is converted to the acetonide protected sulfone **118** which can then be employed as a masked “aldehyde equivalent” in reactions with nucleophiles, such as phenylmagnesium bromide (see Scheme 57). This avoids the need to handle configurationally unstable aldehydes and allows access to aldehyde equivalents that are acid-stable.



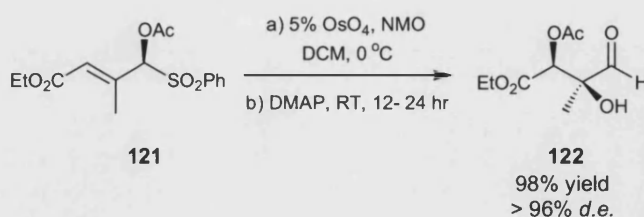
Scheme 57. Chiral sulfones as masked aldehyde equivalents

Attempts to directly liberate the chiral aldehyde from the acetonide protected sulfone **118** gave mixed results. Compounds derived from a di-substituted alkene led to epimerisation of the α -stereocentre or decomposition under a range of basic conditions.^[90] For compounds derived from tri- or tetra-substituted olefins such as **119** however, the use of potassium carbonate and methanol allowed hydrolysis to the α,β -acetonide aldehyde **120** in excellent yield and without racemisation of its stereocentres (see Scheme 58).



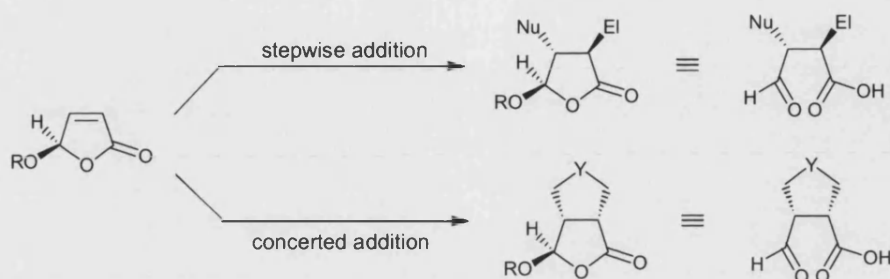
Scheme 58. Liberation of chiral aldehyde from α -acetoxysulfone

One of the disadvantages of using a chiral aldehyde equivalent is the need for an extra step in formation of the sulfone in comparison to a direct enantioselective reaction on the alkene. However, the recent development of a one-pot dihydroxylation, differential protection and aldehyde unmasking strategy overcomes this, allowing access to some diol products that cannot be synthesised by asymmetric dihydroxylation of the corresponding enals.^[90] The α -acetoxysulfones **121** are treated with catalytic osmium tetroxide and NMO to affect the dihydroxylation as before, followed by addition of 4-dimethylaminopyridine to facilitate 1,3-acyl migration, yielding the differentially protected aldehydes **122** as a single product in good yield and high diastereomeric excess ($> 96\%$ *d.e.*) as shown in Scheme 59.



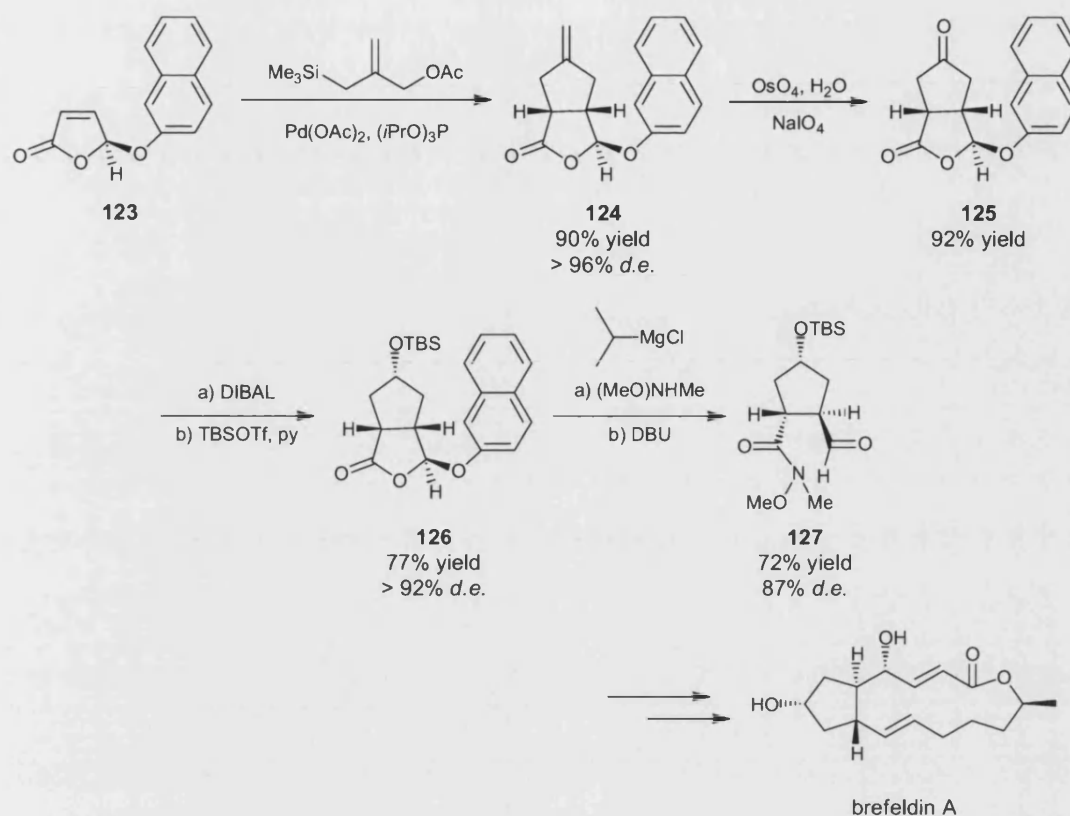
Scheme 59. One-pot dihydroxylation-differential protection unmasking strategy

Another class of chiral aldehyde equivalent are chiral γ -aryloxybutenolides whose C-4 stereocentre can direct either stepwise or concerted addition of nucleophiles to yield products that are masked aldehyde-carboxylic acids (see Scheme 60).



Scheme 60. Hydroxybutenolides as chiral aldehyde equivalents

These compounds were originally developed by Feringa *et al.* using menthol as a chiral auxiliary for their synthesis.^[91] More recently, Trost *et al.* have introduced hydroxybutenolide **123** which is prepared using a palladium catalysed asymmetric allylic alkylation in a dynamic kinetic asymmetric transformation.^[92] They showed that this lactone could undergo Michael additions (stepwise) and cycloadditions (concerted) with a range of nucleophiles or dipolarophiles in good yield and high diastereoselectivity. The cycloaddition strategy was used for the synthesis of brefeldin A, a natural product with a range of biological activity, as shown in Scheme 61. The [3+2] cycloaddition of a trimethylenemethane precursor with chiral butenolide **123** gave bi-cyclopentene **124** which was then treated with catalytic osmium tetroxide and sodium periodate to give ketone **125**. Ketone **125** was then chemo- and diastereoselectively reduced and silyl-protected to compound **126** which was ring opened to aldehyde/Weinreb amide **127** which was a key intermediate in the synthesis of brefeldin A.



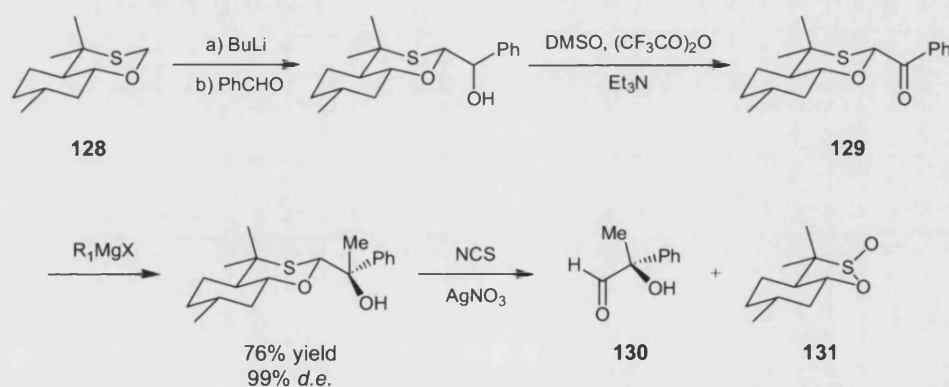
Scheme 61. Use of hydroxybutenolide **123** as an aldehyde equivalent in the synthesis of brefeldin A

Therefore, the use of hydroxybutenolides as aldehyde equivalents is complementary to the use of acetoxysulfones, allowing both nucleophilic and electrophilic additions to functionalise chiral aldehydes.^[90]

1.3.7 Chiral auxiliaries

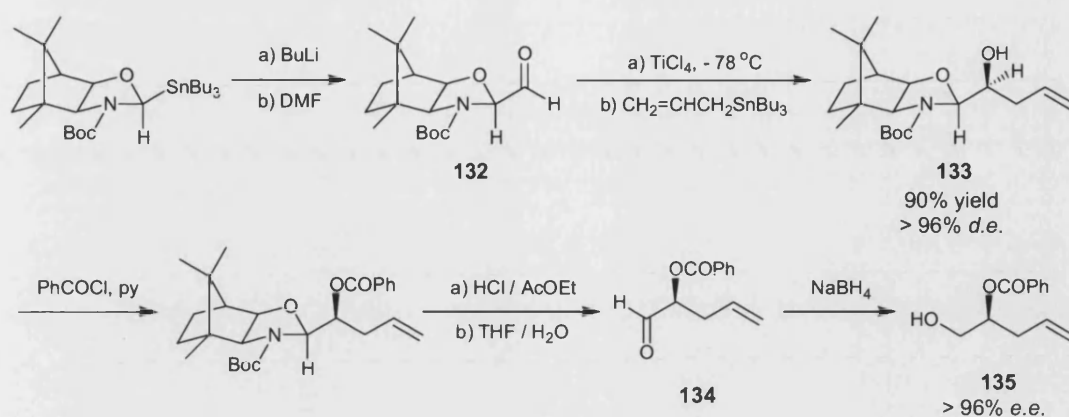
Chiral auxiliaries are often used for the synthesis of chiral aldehydes due to the ability of a masked aldehyde functionality to govern the diastereoselective transformation of a prochiral group within a substrate. Most of these strategies rely on cleavage of a transformed substrate to a chiral alcohol which is then oxidised to a chiral aldehyde, or reduction of an acid derivative to yield a chiral aldehyde, as described earlier. However, there are several examples of the use of chiral auxiliaries in the synthesis of chiral aldehydes which do not require oxidative or reductive methods. Eliel *et al.* have developed a chiral 1,3-oxathiane **128** which is converted to chirally pure 2-acyl derivatives by an aldol type reaction with an aldehyde, followed by oxidation of the resultant alcohol with

DMSO and $(\text{CF}_3\text{CO})_2\text{O}$.^[93] These chiral ketones **129** can then be reacted with a range of Grignard reagents with high diastereoselectivity (generally $> 90\%$ *d.e.*) and then cleaved to give chiral tertiary α -hydroxy aldehydes **130** with good enantioselectivity ($> 94\%$ *e.e.*) via treatment with NCS and silver nitrate as shown in Scheme 62. The reaction also yields oxathiane-derived sultine **131** which can be recycled to the original oxathiane **128** in excellent yield. The chiral α -hydroxy aldehydes could be isolated, but were found to be very unstable and were therefore directly converted into either their corresponding chiral alcohol by reduction with sodium borohydride, or selectively oxidised to their corresponding α -hydroxy acid by treatment with iodine, potassium hydroxide and methanol, with no loss of enantiomeric excess. Both enantiomers of chiral product could be obtained by either reversing the order of introduction of the R and R₁ groups (see Scheme 62), or by using the opposite diastereomer of oxathiane **128**.



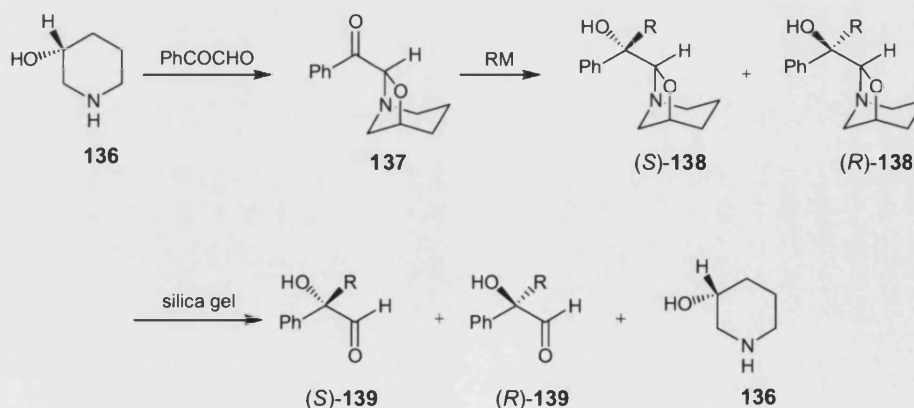
Scheme 62. Use of oxathiane **128** as a chiral auxiliary for the synthesis of chiral α -hydroxy aldehydes

Colombo *et al.* have developed norephedrine and camphor derived 2-acyl-*N*-BOC-oxazolidines as chiral auxiliaries for the asymmetric synthesis of chiral α -hydroxyaldehydes.^[94,95] They may be converted into chiral aldehydes **132** which react with a range of Grignard reagents or allyltributylstannanes in reasonable yield (54 – 90%) and excellent diastereoselectivity, especially in the presence of strong Lewis acids to promote chelation (generally $> 96\%$ *d.e.*).^[96] The resulting chiral alcohol **133** was *O*-benzoyl protected before the chiral aldehyde **134** was released by hydrolysis with dilute acid and immediately reduced to the more stable chiral alcohol **135** with sodium borohydride in high enantiomeric excess (see Scheme 63).



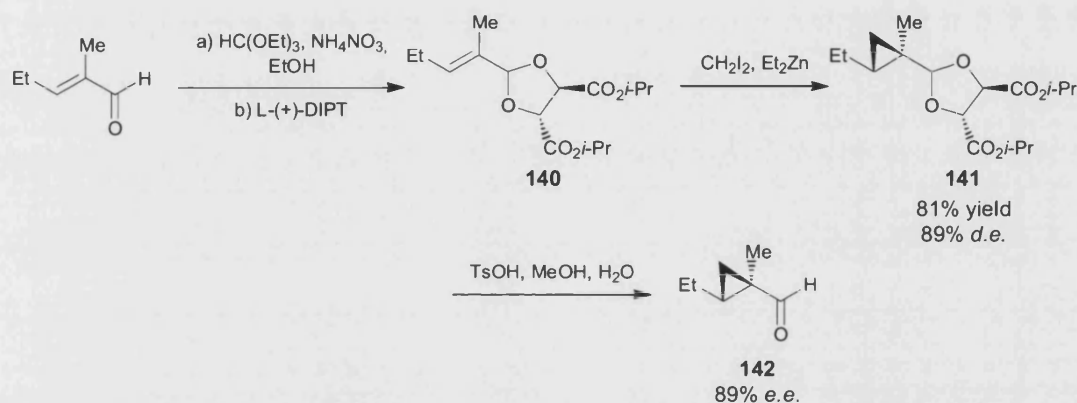
Scheme 63. Camphor derived auxiliary for the synthesis of α -hydroxy aldehydes

A similar piperidin-3-ol auxiliary **136** has been used Chung *et al.* for the synthesis of α -hydroxy aldehydes.^[97] The chiral piperidine derived auxiliary was reacted with phenylglyoxal monohydrate to yield the bridged 2-acyl-1,3-oxazolidine **137** which was then treated with a range of Grignard reagents or organolithiums to yield a diastereomeric mixture of chiral alcohols (*S,S*)-**138** and (*S,R*)-**138** in good yield (generally > 83%). Interestingly, it was found that addition of Grignard reagents favoured formation of an (*S*)-configured alcohol **139** with high diastereoselectivity (86 – 96% *d.e.*), whereas use of organolithiums resulted in formation of the (*R*)-alcohol **139** with lower stereoselectivity. Both enantiomers of the chiral aldehyde could be released by treatment with silica gel in DCM in good enantiomeric excess, allowing for efficient and easy access to a range of α -hydroxy aldehydes (see Scheme 64).



Scheme 64. (*R*)-Piperidin-3-ol as a chiral auxiliary for the synthesis of α -hydroxy aldehydes

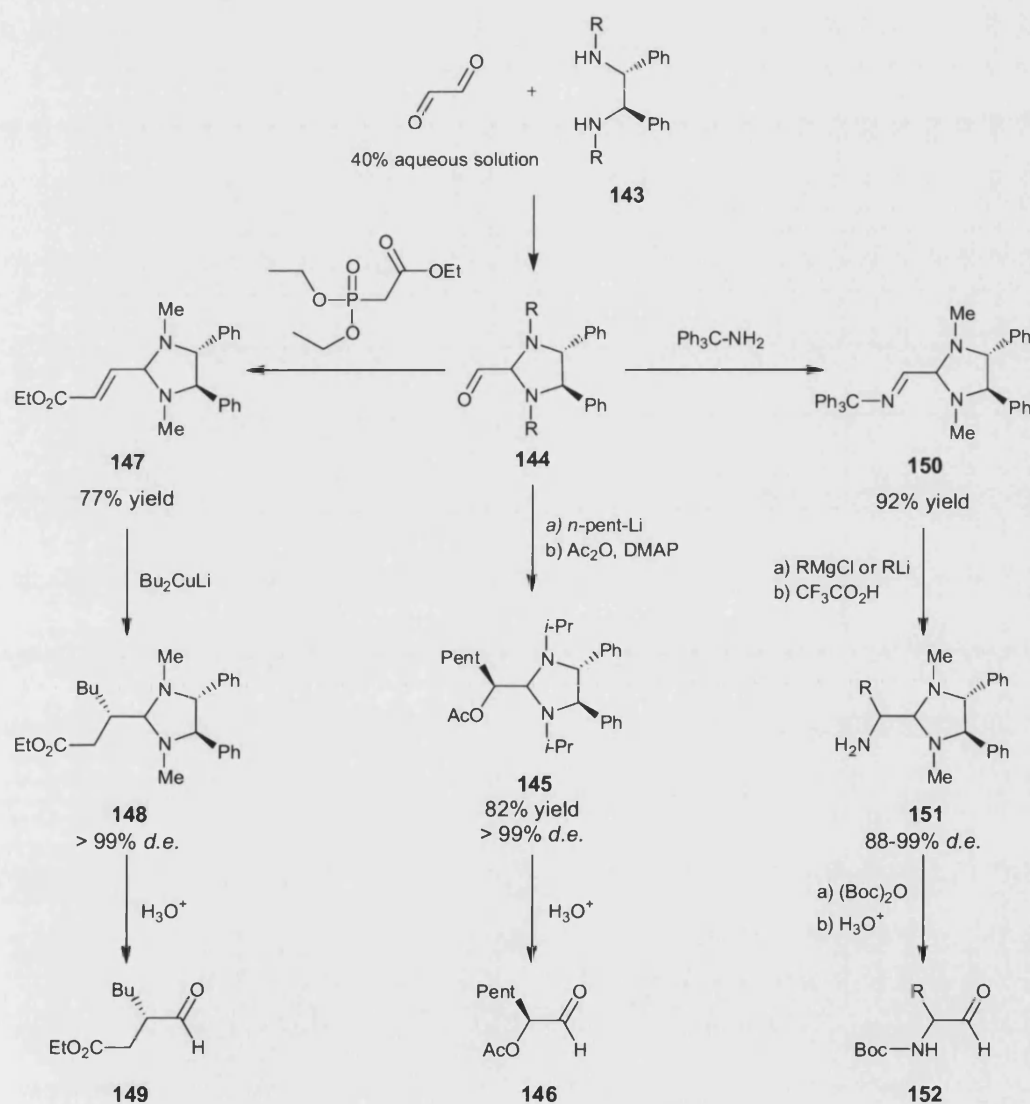
Another class of compounds often used as chiral auxiliaries for the synthesis of chiral aldehydes are acetals.^[98] For example, Yamamoto *et al.* have used chiral diisopropyl tartrate and diethyltartrate to form enantiopure acetals **140** with a range of α,β -unsaturated aldehydes.^[99] The tartrate ligand then controls a Simmons-Smith reaction to yield cyclopropane **141** in reasonable yield (50 - 95%) and high diastereoselectivity (85 - 94%). The chiral aldehyde **142** was released by simple hydrolysis with *para*-toluenesulfonic acid and water without any loss of enantiopurity (see Scheme 65). Since both (*R,R*)- and (*S,S*)-enantiomers of tartaric acid are readily available, synthesis of either enantiomer of chiral aldehyde is easy and predictable.



Scheme 65. Diisopropyl tartrate controlled asymmetric synthesis of cyclopropane aldehydes

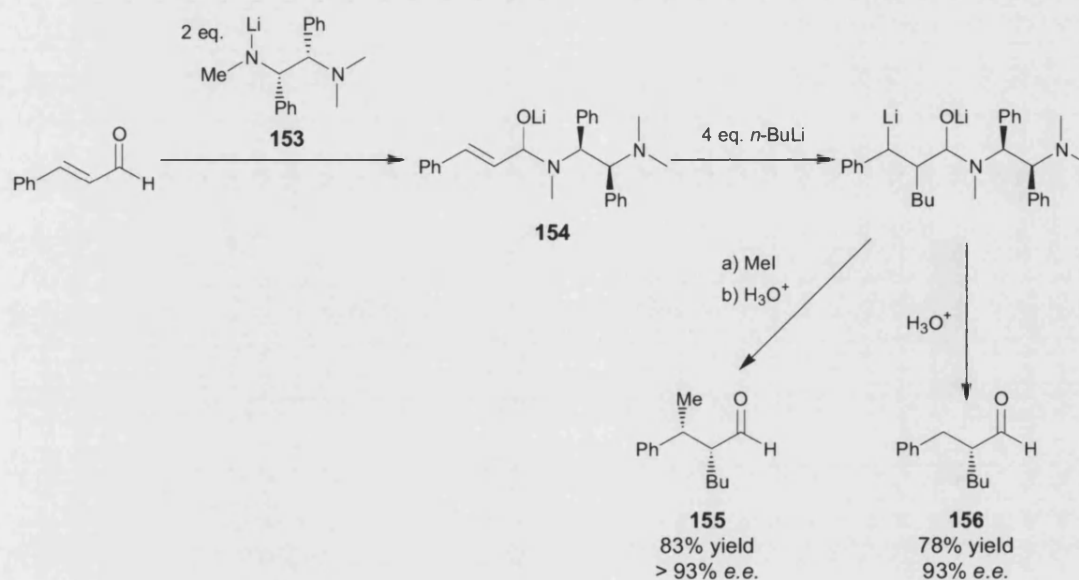
Chiral imidazolidines are the nitrogen equivalents of chiral acetals which can also act as chiral auxiliaries for the synthesis of chiral aldehydes. They have some advantages over acetals since imidazolidines are formed without the need for catalysts, and can be hydrolysed back to their parent aldehyde under mild conditions without racemisation.^[100] Chiral amins have been used widely for the synthesis of chiral aldehydes, with Alexakis *et al.* having reacted chiral diamine **143** with aqueous glyoxal to form amina **144** in 90% crude yield, which was then used to direct several different transformations.^[101] Reaction with organolithiums, followed by acetyl protection of the hydroxyl group proceeded in good yield and forms a single diastereomer of amina **145** which could be hydrolysed to α -acetoxy aldehyde **146** with no loss of enantiomeric excess (see Scheme 66). Amina **144** also underwent a Wadsworth-Emmons olefination to yield (*E*)- α,β -unsaturated ester **147** followed by conjugate addition of cuprates to yield **148** with complete diastereocontrol. Hydrolysis of this adduct **148** afforded chiral aldehyde **149** with no appreciable

racemisation. The aminoral could also be transformed into imine **150** via treatment with primary amines such as tritylamine, which reacted with organolithium reagents to afford a single diastereomer of adduct **151** in good yield,^[102] whereas treatment with Grignard reagents led to formation of the opposite stereocentre in adduct **151**.^[103] Subsequent removal of the *N*-trityl group and *N*-Boc protection, followed by mild acid hydrolysis released chiral α -amino aldehydes (*R*)-**152** in reactions with organolithiums and (*S*)-**152** with Grignard reagents.



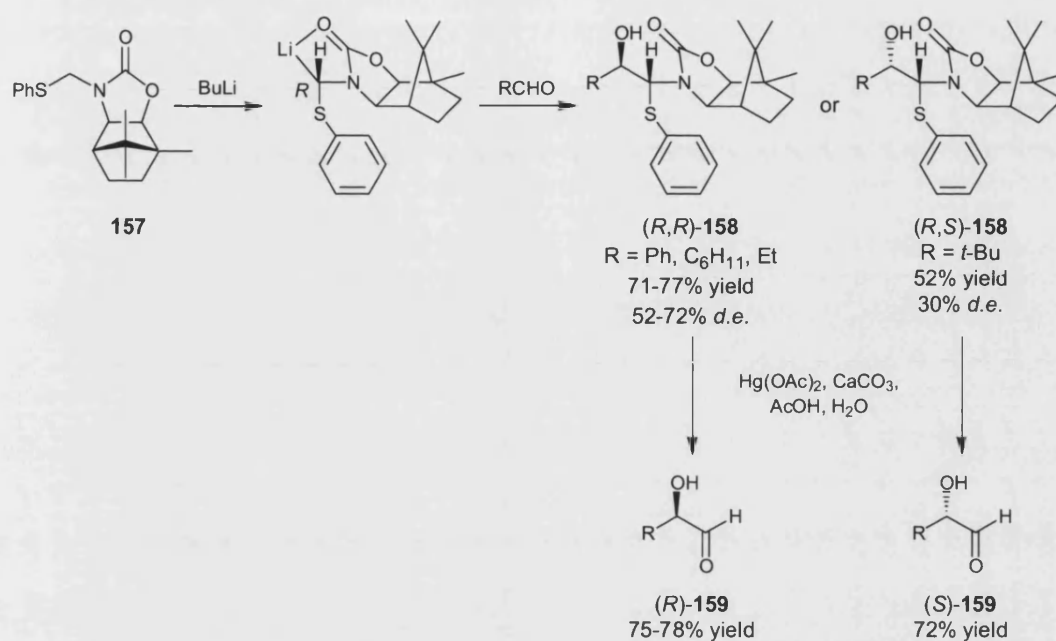
Scheme 66. Aminals as chiral auxiliaries in the synthesis of chiral aldehydes

More recently Normant *et al.* have developed a chiral lithium amide **153** which can be added to prochiral aldehydes such as cinnamaldehyde to form an aminoalkoxide **154**.^[104] Addition of various organolithium reagents resulted in a regio- and stereoselective carbolithiation which can lead to the synthesis of α -mono **155**, or α,β -disubstituted **156** aldehydes on quenching with either acid/water or methyl iodide in good yield and enantiomeric excess (see Scheme 67).



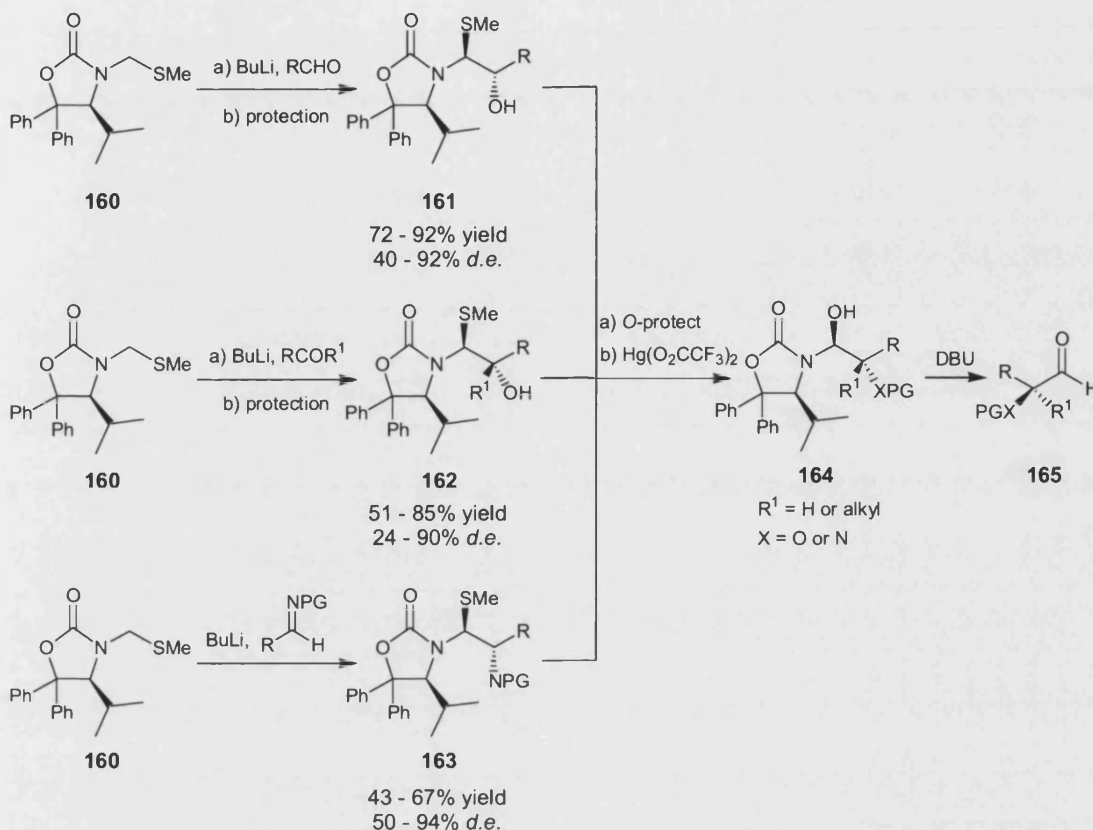
Scheme 67. Lithium amide **153** mediated carbolithiation for the synthesis of chiral aldehydes

Gawley *et al.* have developed a camphor-derived auxiliary **157** which can be lithiated and added to a range of aldehydes to afford crystalline adducts **158** which simplifies the purification of diastereomers.^[105] It was found that addition of auxiliary **157** to benzaldehyde, cyclohexane and propanal resulted in attack at the *Si* face of the aldehyde to yield adduct (*R,R*)-**158** in good yield and diastereoselectivity, whereas addition to pivaldehyde occurred with lower selectivity to the *Re* face of the aldehyde to produce (*R,S*)-**158** (see Scheme 68). Mercury assisted hydrolysis released both enantiomers of chiral α -hydroxyaldehyde **159** in good yield depending on the choice of prochiral aldehyde.



Scheme 68. Camphor derived auxiliary **157** in the synthesis of α -hydroxyaldehydes

Seebach *et al.* have developed a novel thiomethyl oxazolidinone **160** which can be used for the enantioselective nucleophilic formylation of carbonyl compounds.^[106] Lithiation of **160** followed by treatment with aldehydes, ketones or imines affords adducts **161**, **162** and **163**, in moderate to excellent yield and good diastereoselectivity. After selective protection of the hydroxyl functionalities, these adducts could be hydrolysed to yield hemiaminal intermediate **164** which collapsed to chiral aldehyde **165** on treatment with DBU (see Scheme 69).



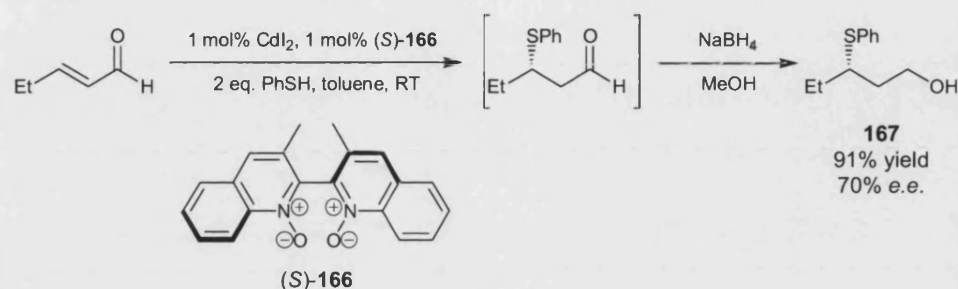
Scheme 69. Methylthiomethyl oxazolidinone **160** as a chiral auxiliary for the synthesis of chiral aldehydes

Although chiral auxiliaries have been widely used for the asymmetric synthesis of chiral aldehydes, the range of functionalities that has been incorporated into these non-reductive/oxidative strategies is still fairly limited and there is still much potential for further work in this area.

1.3.8 Conjugate additions and cycloadditions to α,β -unsaturated aldehydes

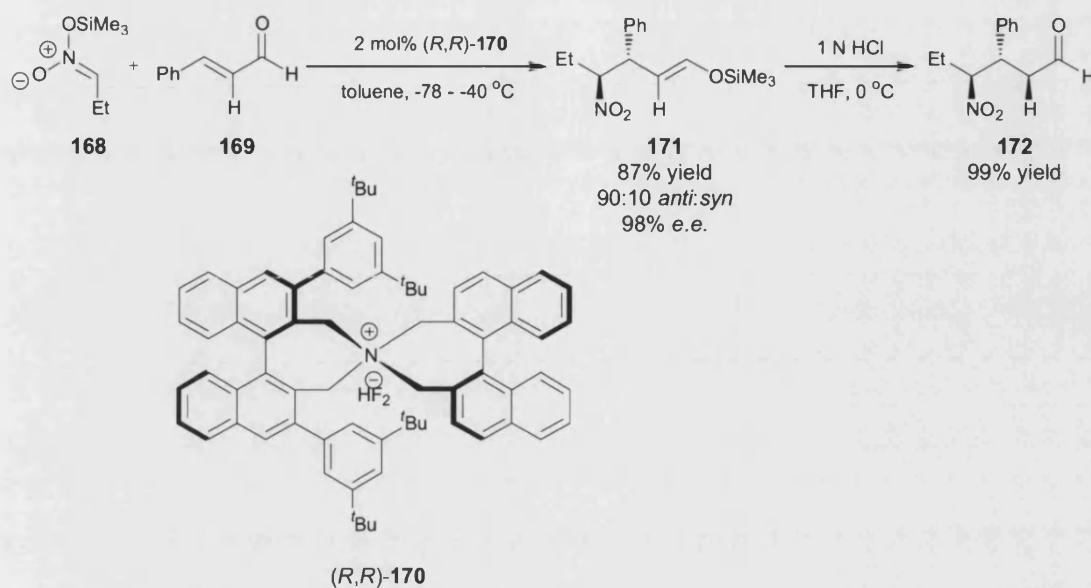
Conjugate additions represent a useful carbon-carbon bond forming reaction in asymmetric synthesis, however one of the inherent difficulties associated with 1,4-conjugate additions to unsaturated aldehydes is the propensity of the aldehyde functionality to undergo competing 1,2-addition pathways. Nakajima *et al.* have developed a cadmium complex of chiral *N,N'*-bis-pyridine-*N*-oxide ligand **166** which can catalyse conjugate additions of thiophenol to enals in good yield and enantioselectivity, after reduction to their more stable chiral alcohols **167** in situ (see Scheme 70).^[107,108] The mildness of these conditions

overcomes the usual lability of the aldehyde functionality allowing for the first reported enantioselective conjugate additions of thiols to enals, in addition to being the first report of a cadmium complex being used in an enantioselective reaction.



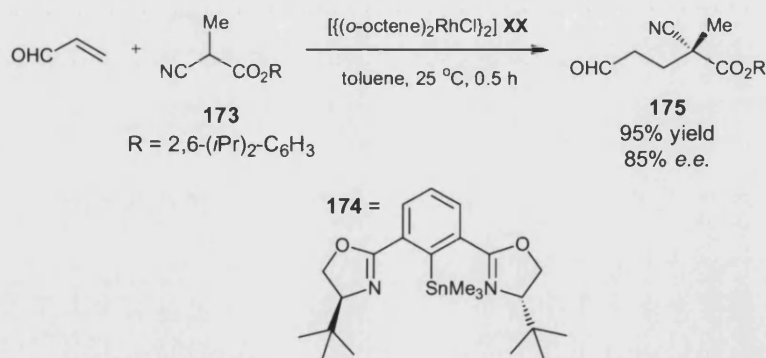
Scheme 70. Enantioselective conjugate addition of thiophenol to enals catalysed by CdI_2 -**166**

Maruoka *et al.* have found that a chiral quaternary ammonium bifluoride complex **170** could control the regio- and stereo-chemistry of fluorine catalysed Michael addition of silyl nitronates **168** to α,β -unsaturated aldehydes **169** via formation of chiral ammonium nitronate intermediates in situ.^[109] Tuning of the ligand structure allowed conditions to be identified that afforded a highly selective 1,4-addition reaction (32:1, 1,4-:1,2-addition).^[110] The reaction yields stable enol silyl ethers **171** in excellent yield and enantioselectivity, which could be converted into chiral γ -nitro aldehydes **172** via treatment with acid with no loss of enantiomeric excess. Another useful feature of this reaction is that protonation of enol silyl ether **171** containing an α -substituent can be carried out diastereoselectively by simple treatment with HCl at 0 °C to exclusively furnish chiral aldehyde **172** containing three contiguous stereocentres (see Scheme 71).



Scheme 71. Asymmetric Michael addition of silyl nitronates to α,β-unsaturated aldehydes catalysed by chiral quaternary ammonium bifluoride **170**

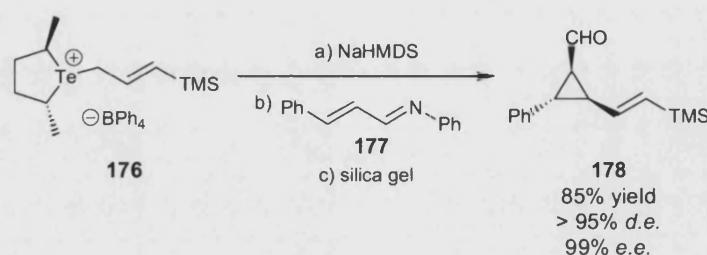
Motoyama *et al.* have reported the novel asymmetric Michael addition of α-cyanopropionates to acrolein using the Phebox-derived **174** rhodium(III) catalyst.^[111] The best enantioselectivities were achieved with α-cyanopropionates containing bulky ester groups such as **173** affording chiral aldehyde **174** containing a γ-stereocentre in excellent yield over short reaction times (see Scheme 72).



Scheme 72. Michael addition of α-cyanopropionates to acrolein

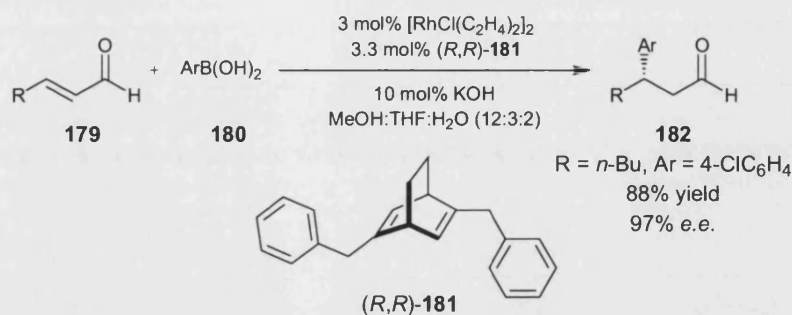
The tandem Michael addition-elimination of sulfur or tellurium ylides to electron deficient olefins is a useful strategy for the synthesis of functionalised cyclopropanes. This reaction

has been previously reported for the enantioselective cyclopropanation of esters, amides, ketones and nitriles,^[112-114] however the reactivity of the aldehyde functionality makes the synthesis of their corresponding cyclopropane aldehydes difficult due to the presence of a competing epoxidation mechanism. To overcome this problem, Tang *et al.* have used α,β -unsaturated imines in enantioselective cyclopropanations with tellurium ylides.^[115] Thus telluronium salt **176** undergoes deprotonation with NaHMDS followed by conjugate addition to imines **177**, to afford an adduct which on exposure to damp silica gel afforded chiral cyclopropane aldehydes **178** in good yield and excellent selectivity (see Scheme 73).



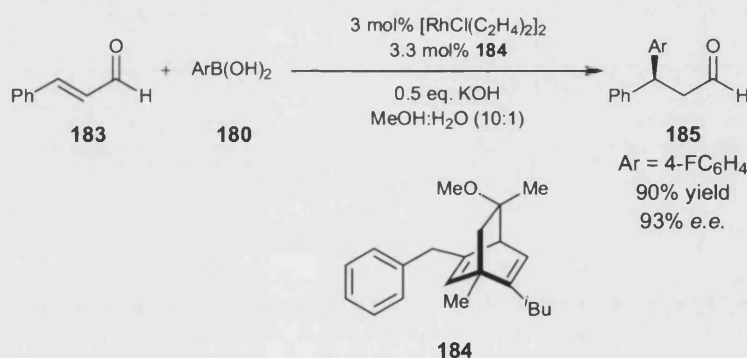
Scheme 73. Asymmetric cyclopropanation of α,β -unsaturated imines **177** with tellurium ylide **176**

Recently Hayashi *et al.* have reported the rhodium catalysed asymmetric 1,4-addition of arylboronic acids to α,β -unsaturated aldehydes mediated by a chiral diene ligand **181**.^[116] Optimisation of ligand and conditions maximised the yield of the 1,4-addition pathway enabling a range of electron-rich and electron-deficient arylboronic acids **180** to be used for the synthesis of a range of chiral aldehydes **182** in excellent yield and enantiomeric excess (see Scheme 74). This reaction allowed access to both enantiomers of chiral aldehyde **XX** using the same enantiomer of chiral ligand **181**, simply by altering the sequence of substituents on the aldehyde and boronic acid. The (*S,S*)-enantiomer of chiral diene ligand **181** was also used for the 1,4-addition of arylboronic acids to α,β -unsaturated Weinreb amides in high yield (74 – 93%) and excellent enantioselectivity (80 – 92% e.e.).^[117]



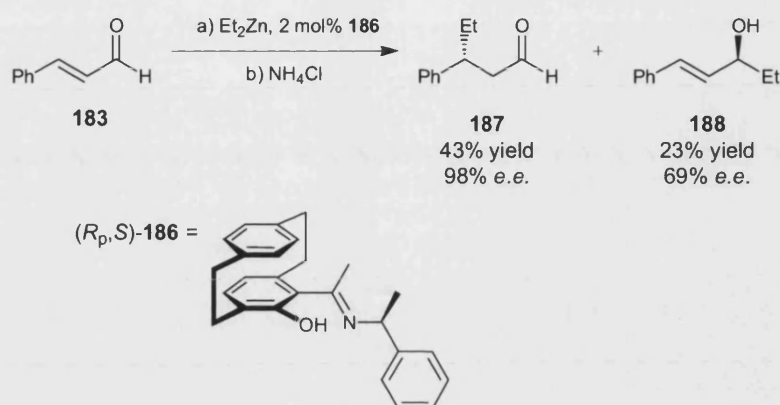
Scheme 74. Asymmetric conjugate addition of arylboronic acids to α,β -unsaturated aldehydes mediated by Rh/(*R,R*)-181

In the same year Carreira *et al.* reported a related chiral diene ligand **184** to affect this type of rhodium catalysed addition of electron rich and electron poor arylboronic acids to substituted cinnamaldehydes **183** in good yield (63 – 90%) and excellent enantioselectivity (89 – 93% e.e.) (see Scheme 75).^[118]



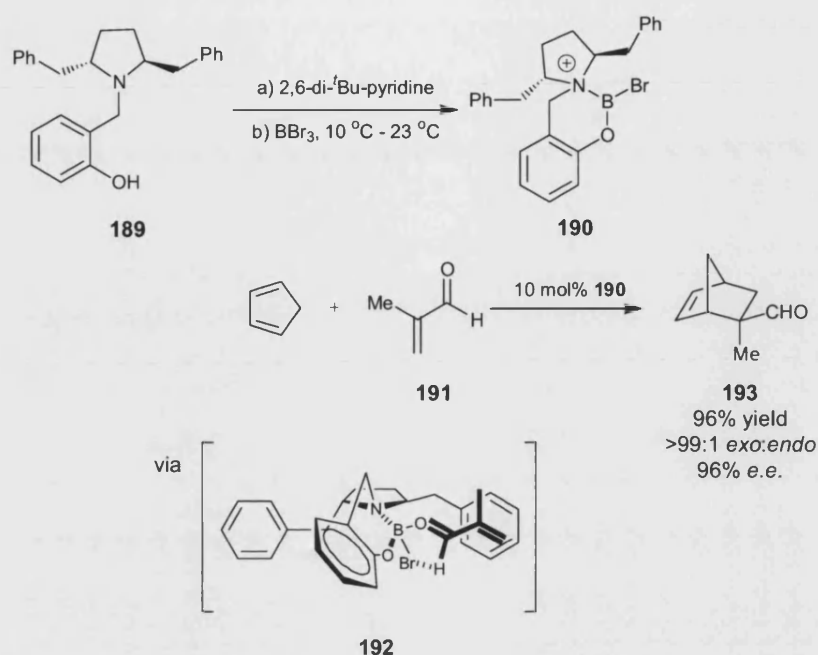
Scheme 75. Asymmetric conjugate addition of arylboronic acids to substituted cinnamaldehydes mediated by Rh/184

The asymmetric 1,4-addition of organozinc reagents to α,β -unsaturated aldehydes without the need for a metal catalyst has recently been reported by Brase *et al.*^[119] For example cinnamaldehyde **183** was treated with diethylzinc in the presence of chiral ligand (*R_p*,*S*)-**186** to afford the corresponding 1,4-addition product **187** in excellent 98% e.e. (see Scheme 76). Unfortunately yields were moderate (43%) due to competing formation of the 1,2-addition product **188**, however this was reduced in more sterically demanding substrates.



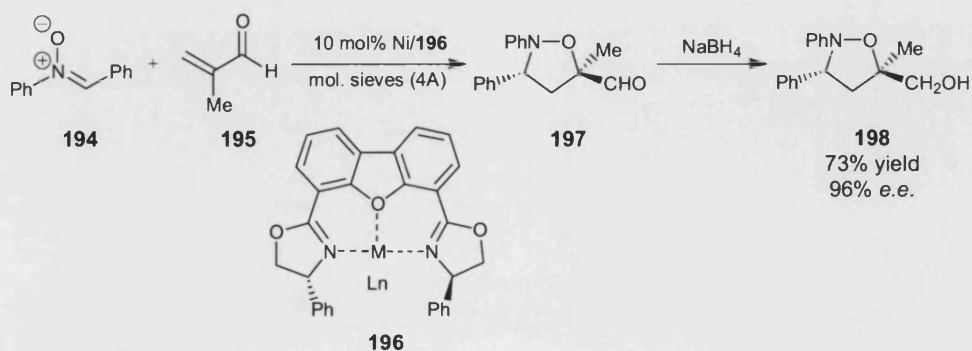
Scheme 76. Asymmetric 1,4-conjugate addition of diethyl zinc to cinnamaldehyde without the need for metal salts

Corey *et al.* have developed a cationic chiral catalyst for the enantioselective Diels-Alder reaction of α,β -enals with cyclopentadiene.^[120] Chiral amino phenol ligand **189** was complexed to boron to generate a chiral Lewis acid **190** in situ, which was used to control addition of dienes to the *Si* face of the dienophile through transition state **192**. For example, addition of cyclopentadiene to aldehyde **191** proceeds in excellent yield and selectivity to give chiral aldehyde **192** (see Scheme 77) and chiral ligand **189** which can be recovered and reused. This type of Diels-Alder transformation has also been carried out successfully using chiral Lewis acid complexes of ruthenium,^[121] iron,^[122] indium,^[123] and cobalt,^[124] as well as tartaric acid derived chiral (acyloxy)borane (CAB) catalysts,^[125] Brønsted acid-assisted Lewis acid (BLA),^[126] and Lewis acid-assisted Lewis acid (LLA) chiral catalysts.^[127]

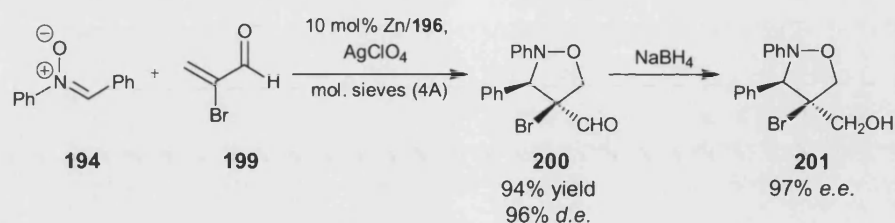


Scheme 77. Chiral Lewis acid catalysed enantioselective Diels-Alder

Kanemasa *et al.* have developed a chiral DBFOX/Ph complex **196** which was effective in enantioselective nitron cycloadditions with α,β -unsaturated aldehydes.^[128] In reactions with α -alkyl and α -aryl acroleins with nitron **194** the nickel (II) or magnesium complexes afforded isoxazolidine-5-carbaldehydes **197** by steric control. For example reaction of methacrolein **195** with nitron **194** at room temperature in the presence of nickel(II)**196** complex afforded a single diastereomer of aldehyde **197** which was reduced in situ to afford chiral alcohol **198** in good yield and enantioselectivity (see Scheme 78). However when α -bromoacrolein **199** was reacted with a range of nitrones **194** it was found that isoxazolidine-4-carbaldehydes **200** were successfully formed using a zinc (II) complex under electronic control (see Scheme 79).



Scheme 78. Enantioselective nitron cycloaddition with methacrolein catalysed by Ni(II)/**196** complex

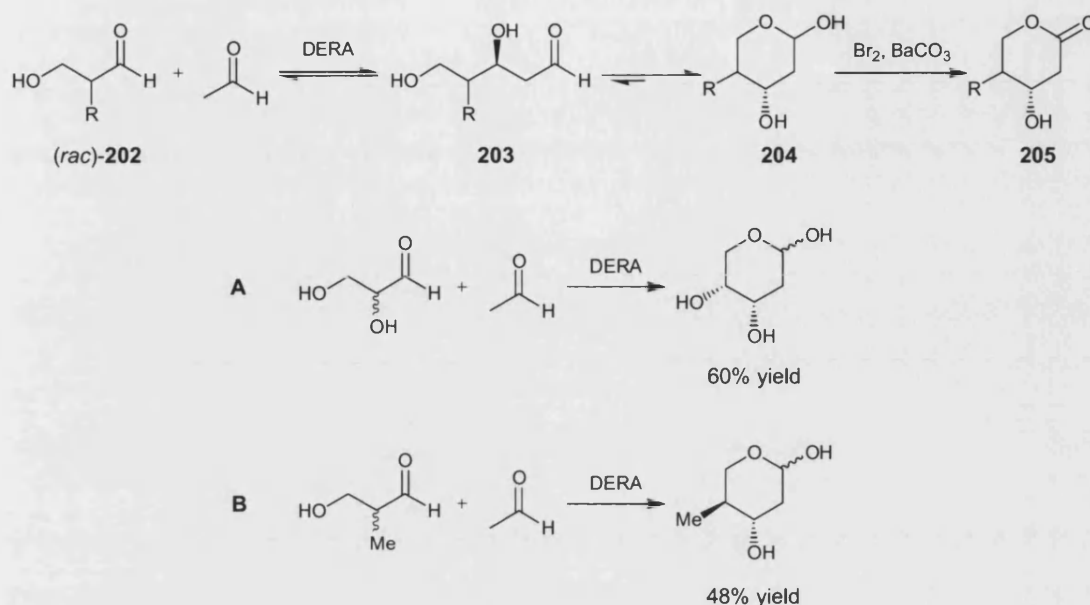


Scheme 79. Enantioselective nitron cycloadditions to α -bromoacrolein catalysed by Zn(II)/**196** complex

Similar enantioselective 1,3-dipolar cycloadditions have been reported using catalysts based on ketoiminato cobalt(III),^[129] copper(I)-Fesulphos,^[130] titanium-BINOLates,^[131] and rhodium- and iridium-Prophos complexes.^[132]

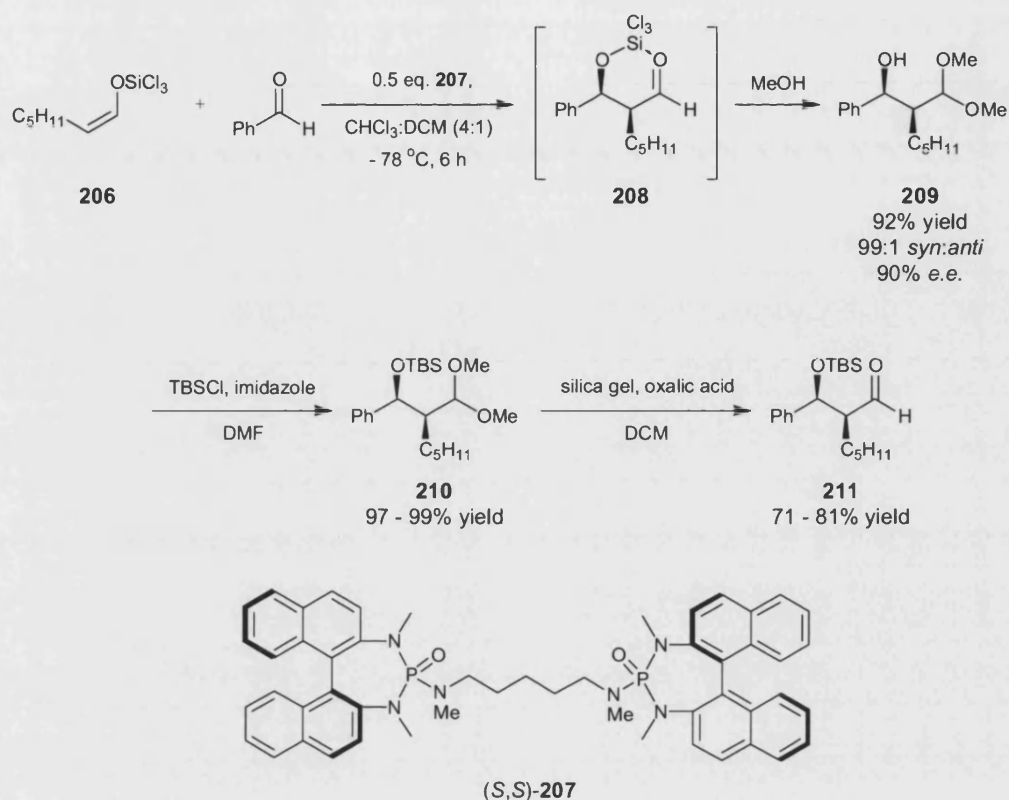
1.3.9 Aldol reactions

Wong *et al.* have developed a new strategy for the synthesis of pyranose synthons using 2-deoxyribose-5-phosphate aldolase (DERA) for stereoselective aldol reactions.^[133] This enzyme has been shown to effectively catalyse sequential aldol reactions with a range of aldehyde donors and acceptors.^[134,135] This strategy has been exploited for the aldol reaction of the enolate of acetaldehyde with a range of β -hydroxyaldehydes **202** to afford chiral aldehyde **203** which immediately cyclises to form the more stable hemiacetal **204**, thus driving the reaction towards condensation (see Scheme 80). These hemiacetals could be further oxidised to lactones **205** in good yield. Interestingly, it was found that the substituent at the C2 position of the acceptor aldehyde had a marked effect on the stereoselectivity of the reaction allowing kinetic resolutions to be carried out. For example, when a polar group such as OH or N₃ was present the aldolase reacted almost exclusively with the D-isomer (see Scheme 80-A), whereas when a hydrophobic residue, such as a methyl group, was present the selectivity was reversed for the L-isomer (see Scheme 80-B).



Scheme 80. Aldolase catalysed synthesis of pyranose synthons via chiral aldehyde **203**

In 2001, Denmark *et al.* reported the first catalytic enantioselective crossed-aldol reactions of aldehydes using a dimeric chiral Lewis base **207** as a catalyst.^[136] A range of trichlorosilyl enolates such as **206** were reacted with a range of aldehydes to afford crossed-aldol products such as **208** in high yield and moderate to high enantioselectivity, with *syn* or *anti* diastereoselectivity being governed by the (*E*)- or (*Z*)-conformation of the trichlorosilyl enolate. It is thought that these reactions overcome many of the usual problems associated with aldol reactions of aldehydes by chelation of the aldehyde carbonyl to silicon which reduces the Lewis basicity of the aldol product.^[137] The aldol products were immediately protected as their dimethyl acetals **209**, however these could be converted to their TBS protected aldehydes **211** in two high yielding steps with no detectable epimerization (see Scheme 81).

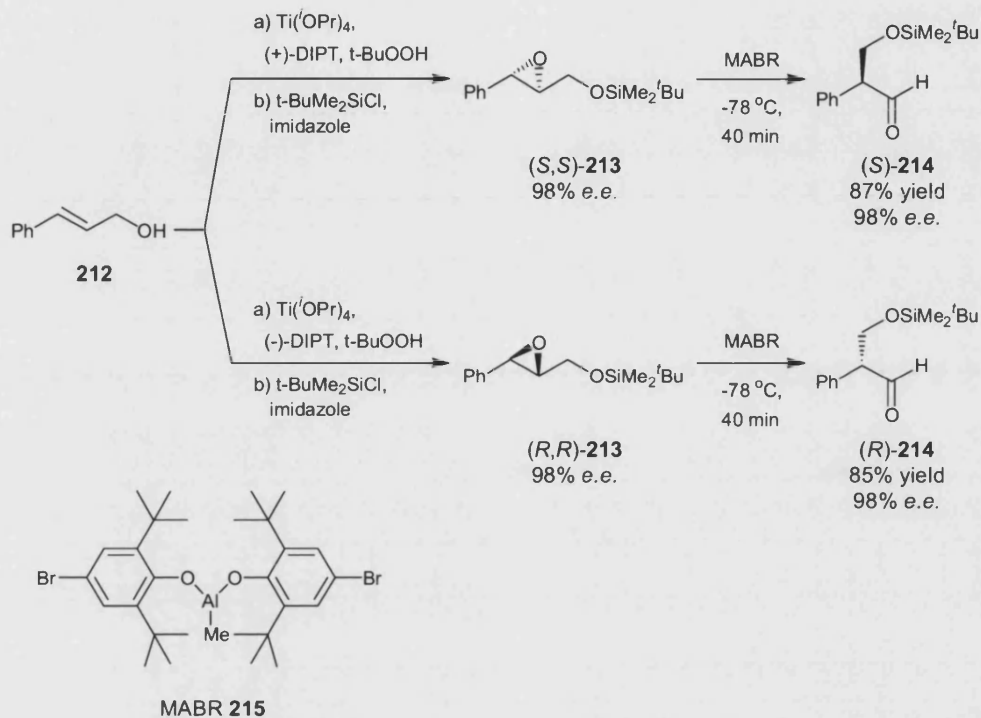


Scheme 81. Enantioselective crossed-aldol reaction catalysed by **207**

1.3.10 Rearrangement reactions

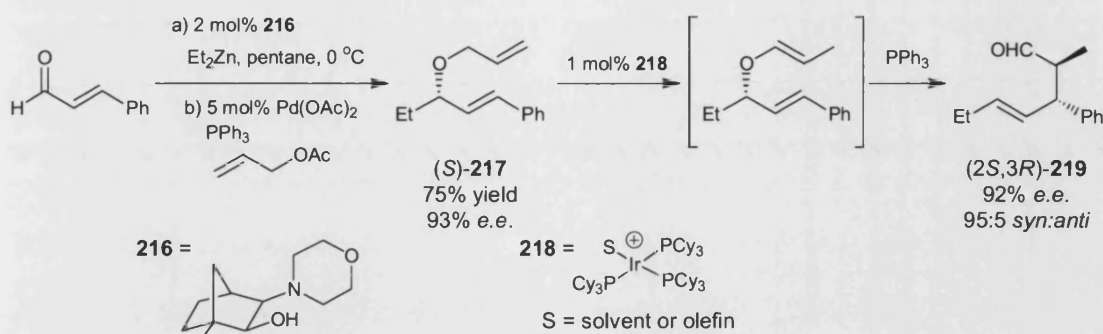
Epoxy silyl ethers are easily accessed from allylic alcohols via the Sharpless asymmetric epoxidation reaction. Yamamoto *et al.* have reported a novel stereocontrolled rearrangement of epoxy silyl ethers to yield β -siloxy aldehydes in good yield and stereocontrol using a bulky organoaluminium Lewis acid catalyst under mild conditions.^[138] For example, Sharpless asymmetric epoxidation of allylic alcohol **212**, followed by silylation gives rise to either enantiomer of epoxide **213** in excellent enantioselectivity. Subsequent treatment of either enantiomer with methylaluminium bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR) **215** afforded either enantiomer of chiral aldehyde **214** in good yield and with no loss of enantioselectivity (see Scheme 82). Although this reaction uses two equivalents of MABR it was possible to reduce the amount to catalytic quantities (up to 10 mol%) with no loss of enantioselectivity. However, the catalytic protocol was found to be less tolerant of a range of substitution on the epoxide fragment. The development of a high valent metalloporphyrin chromium complex

Cr(TPP)OTf has allowed more substituted epoxide fragments to be utilised in these reactions.^[139]



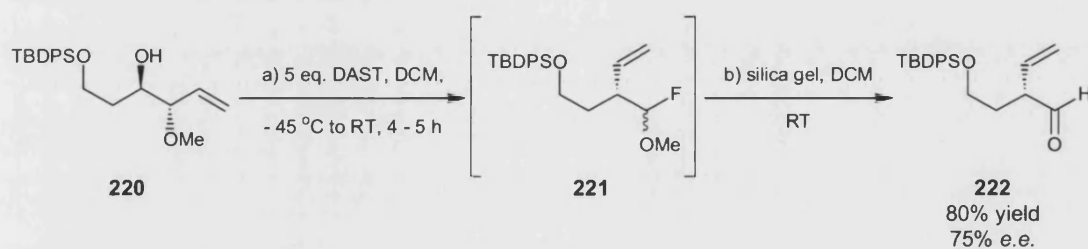
Scheme 82. Organoaluminium promoted rearrangement of epoxides in the synthesis of chiral aldehydes

In 2003 Nelson *et al.* reported the isomerisation-Claisen rearrangement (ICR) reaction catalysed by an iridium phosphine species.^[140] The reaction was optimised to allow (-)-MIB **216** catalysed addition of diethylzinc to cinnamaldehyde and subsequent Pd catalysed *O*-allylation to afford (S)-bis(allyl) ether **217**. This ether subsequently underwent ICR reaction on treatment with iridium phosphine species **218** followed by triphenyl phosphine, which attenuates the Lewis acidity of the iridium complex to prevent epimerisation of the aldehyde stereocentre, to afford pentenal **219** in excellent *syn:anti* diastereoselectivity and high e.e. (see Scheme 83).^[141]



Scheme 83. Isomerisation-Claisen rearrangement reaction catalysed by iridium phosphine species **218**

Recently Cossy *et al.* have reported the rearrangement of homoallylic alcohols induced by diethylaminosulfur trifluoride (DAST).^[142] Treatment of β,γ -unsaturated monoprotected diols such as **220** with DAST allow the stereoselective formation of β,γ -unsaturated aldehydes in good yields and with good transfer of chirality (see Scheme 84). The reaction of homoallylic alcohol **220** with DAST affords homoallylic fluoride **221** which could be isolated and converted to β,γ -unsaturated aldehyde **222** in good yield and enantiomeric excess on exposure to silica gel. The enantioselectivity and configuration of aldehyde **222** was determined by reduction to the alcohol, transformation to the corresponding lactone and comparison to literature data.



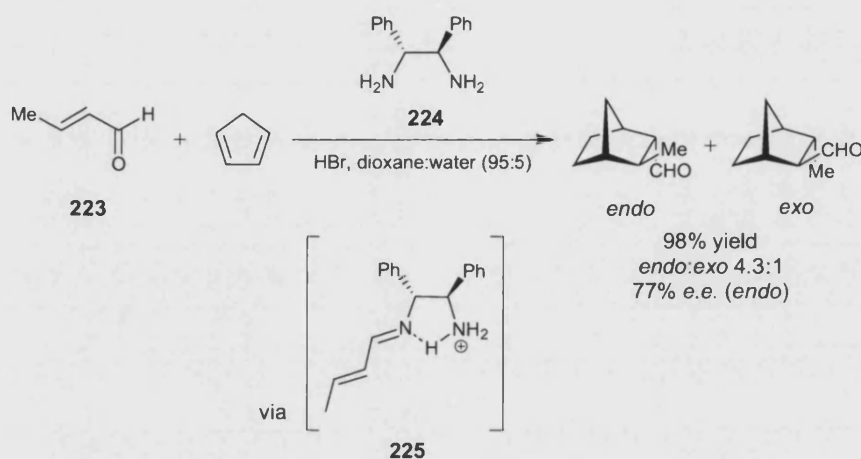
Scheme 84. Rearrangement of homoallylic alcohols by DAST

1.3.11 Organocatalysis

Organocatalysis, the acceleration of chemical reactions using substoichiometric amounts of an organic compound that do not contain a metal atom, is one of the biggest areas of current research in asymmetric synthesis. This area has recently been extensively and exhaustively reviewed^[143-146] and therefore this section will only describe a few

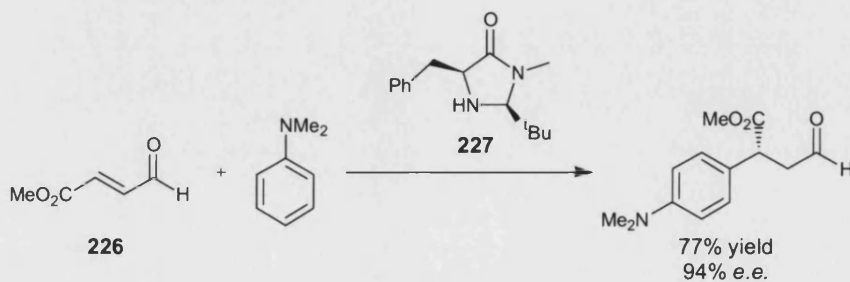
representative examples that highlight the synthetic utility of organocatalysts for the asymmetric synthesis of chiral aldehydes.

Ha *et al.* have developed an organocatalytic Diels-Alder reaction of α,β -unsaturated aldehyde **223** using a chiral 1,2-diamino-1,2-diphenylethane catalyst **224** in excellent yield and good enantioselectivity (see Scheme 85). It was proposed that the enantioselectivity of the reaction is governed via a hydrogen bonded intermediate **225**.



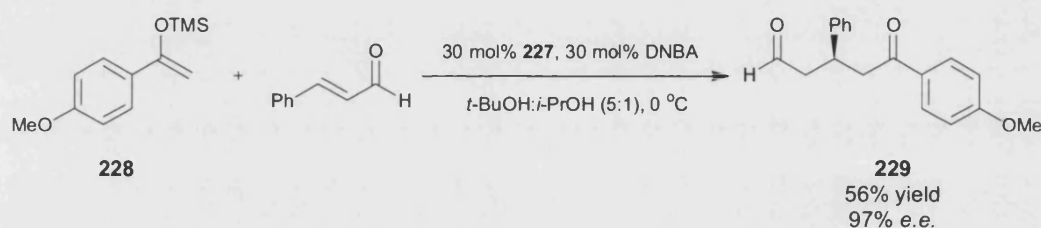
Scheme 85. Organocatalytic Diels-Alder reaction

Macmillan *et al.* have found that formation of an iminium ion conjugated with a double bond lowers the energy of the olefin LUMO, which enables conjugate addition of electron rich aromatic or heteroaromatic rings to α,β -unsaturated aldehydes.^[147-149] For example, using chiral imidazolidinone catalyst **227**, *N,N*-dimethylaniline could be added to unsaturated aldehyde **226** with good yield and excellent enantioselectivity (see Scheme 86).^[149]



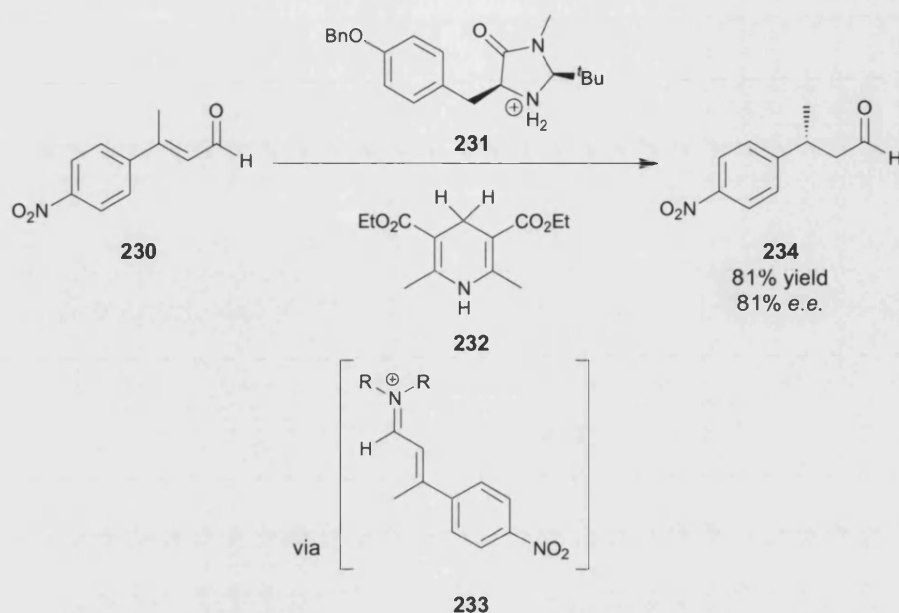
Scheme 86. Organocatalytic conjugate addition

The same imidazolidinone catalyst **227** has been used by Wang *et al.* for the enantioselective Mukaiyama-Michael addition reaction of silyl ethers to α,β -unsaturated aldehydes to afford δ -keto aldehydes containing a β -stereocentre in good yield (56 – 87%) and high enantioselectivities (85 – 97%).^[150] For example silyl enol ether **228** was reacted with cinnamaldehyde in the presence of chiral imidazolidinone **227** and acid additive 2,4-dinitrobenzene sulfonic acid (DNBA) to afford chiral δ -keto aldehyde **229** with excellent 97% enantiomeric excess albeit in moderate yield (see Scheme 87).



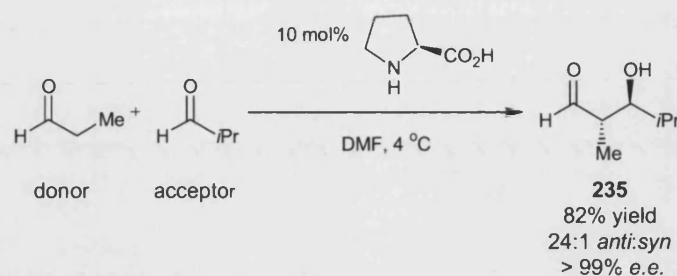
Scheme 87. Mukaiyama-Michael addition reaction for the synthesis of δ -keto aldehydes

Asymmetric hydrogenation of alkene bonds often requires expensive, substrate specific catalysts and high pressures, however List *et al.* have overcome these problems by developing an organocatalytic asymmetric conjugate reduction of α,β -unsaturated aldehyde **230** to form chiral aldehyde **234**.^[151] It is thought that chiral amine **231** catalyses a metal-free transfer hydrogenation of the iminium ion intermediate **233** using Hantzsch ester **232** as a hydride donor (see Scheme 88).



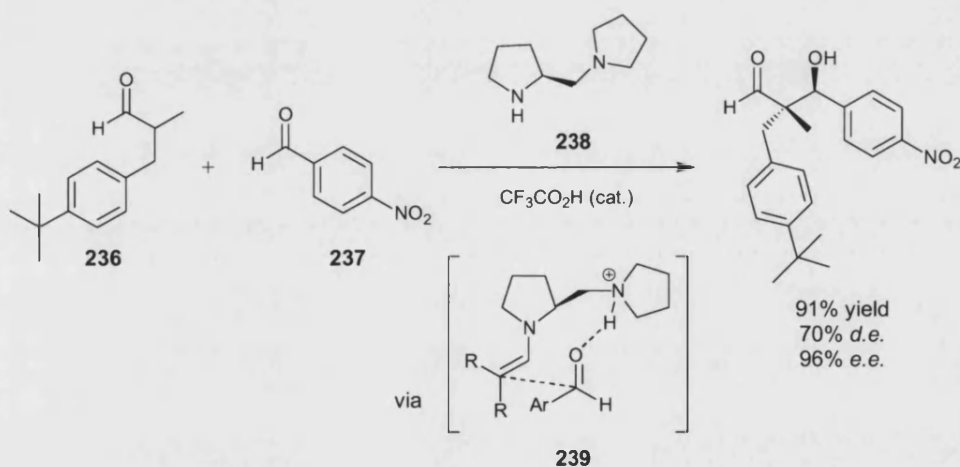
Scheme 88. Organocatalytic transfer hydrogenation

Aldol reactions are extremely powerful carbon-carbon bond forming reactions that can generate two new stereocentres. One of the limitations of this reaction when attempting to react two aldehydes, is that large amounts of homo-coupled products are often formed due to the inherent reactivity of the aldehyde functionality. In 2002 MacMillan *et al.* reported the first direct and enantioselective aldol reaction between two non-equivalent aldehydes, catalysed by L-proline.^[152] It was found that addition of the aldehyde donor to the aldehyde acceptor via a syringe pump was effective in suppressing dimerisation affording the β -hydroxy aldehyde **235** in high yields (75 – 87%) and enantiomeric excess (91 – 99% *e.e.*), a reaction which had previously only been successful using enzymatic catalysis.^[134] A range of aldehyde donors and acceptors were tolerated, including those containing both alkyl and aromatic substituents. Although both aldehyde substrates contain enolisable protons only a single *anti*-diastereomer was formed in high enantiomeric excess (see Scheme 89). This strategy has been extended to the dimerisation of α -oxyaldehydes,^[153] whose aldol products α -oxyaldehydes did not undergo further condensation reactions and instead could be employed in the synthesis carbohydrates by a tandem Mukaiyama aldol addition-cyclisation protocol.^[154]



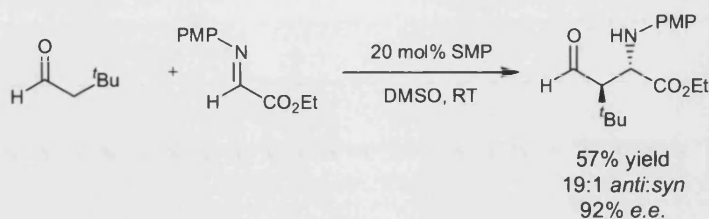
Scheme 89. Proline catalysed direct enantioselective crossed aldol reaction

Tanaka *et al.* have developed this strategy further to allow for the formation of aldol products containing quaternary stereocentres.^[155] Catalyst **238** affects a crossed aldol condensation between α,α -dialkyl aldehyde **236** and electron deficient aryl aldehyde **237** with moderate diastereoselectivity affording the *anti*-aldol in excellent *e.e.* (see Scheme 90). The stereoselectivity is thought to be controlled by the hydrogen bonded transition state **239** which delivers the electron deficient aldehyde to one face of the enamine intermediate.



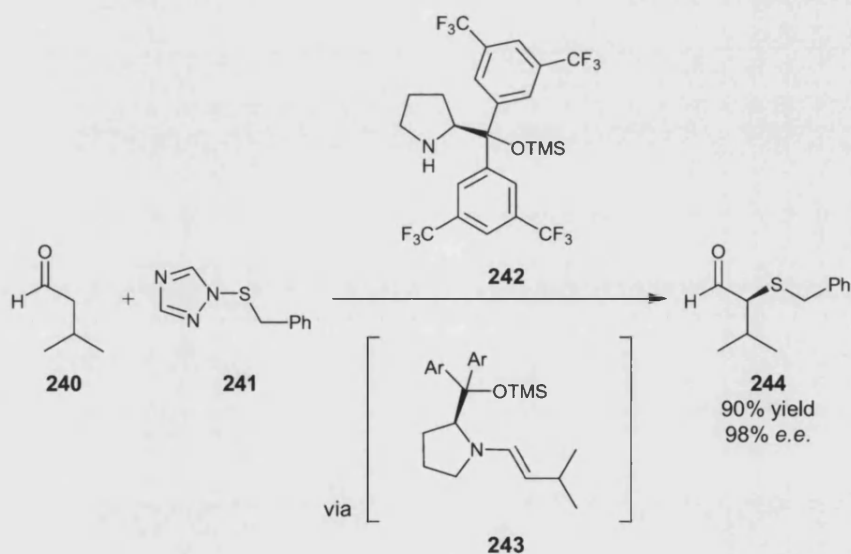
Scheme 90. Organocatalytic crossed aldol condensation

In a similar way (*S*)-2-methoxymethylpyrrolidine (SMP) has been used to catalyse Mannich reactions with preformed imines to synthesise β -amino aldehydes in reasonable yield and good selectivity (see Scheme 91).^[156]



Scheme 91. SMP-catalysed Mannich reaction of aldehydes with PMP-protected α -imino ethyl glyoxylate

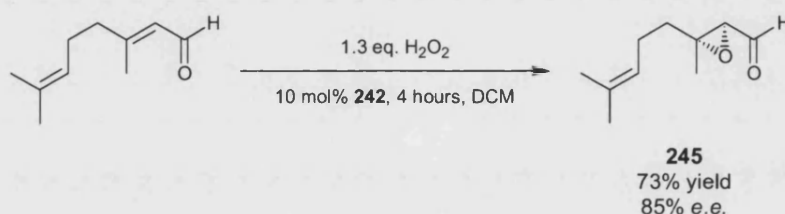
Another strategy for the synthesis of chiral aldehydes is α -substitution. This allows the incorporation of heteroatoms into aldehydes which can be further elaborated to form useful chiral synthons. An example of this is chiral amine **242** catalysed α -sulfenylation of prochiral aldehydes described by Jorgensen *et al.*^[157] Alpha substitution of aldehyde **240** with sulfenylating agent **241** affords α -sulfenyl aldehyde **244** with excellent yield and enantiomeric excess (see Scheme 92) via attack from the *Si* face of enamine intermediate **243**.



Scheme 92. Alpha sulfenylation of prochiral aldehydes

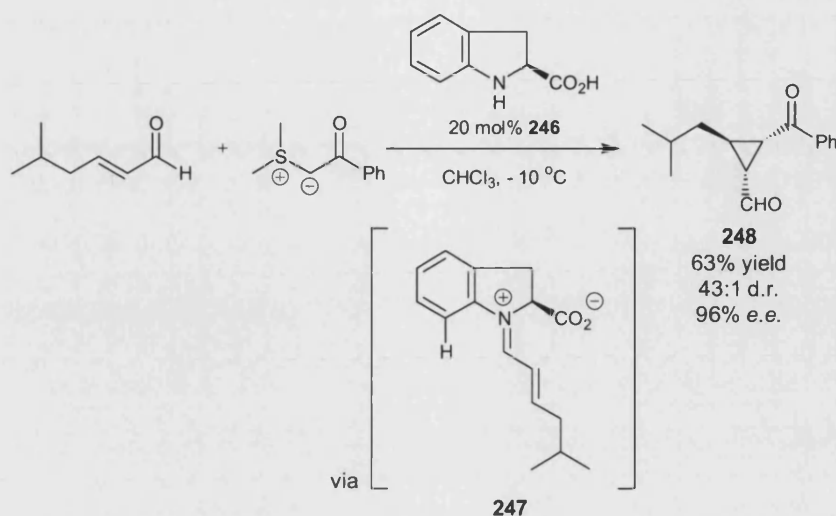
This strategy has also been developed to successfully allow the direct enantioselective α -functionalisation of aldehydes with fluorine,^[158] bromine,^[159] nitrogen and selenium,^[144] and recently γ -amination of α,β -unsaturated aldehydes.^[160]

In 2005 Jorgensen *et al.* extended the use of this catalyst for the first asymmetric organocatalytic epoxidation of α,β -unsaturated aldehydes in good yield (60 – 90%) and excellent enantiomeric excess (mostly > 94% *e.e.*), using hydrogen peroxide as an oxidant.^[161] This methodology has been exploited for the direct synthesis of pheromone **245** as shown in Scheme 93, and the group have further extended this protocol to allow epoxidations to be carried out in alcohol-water solutions.^[162]



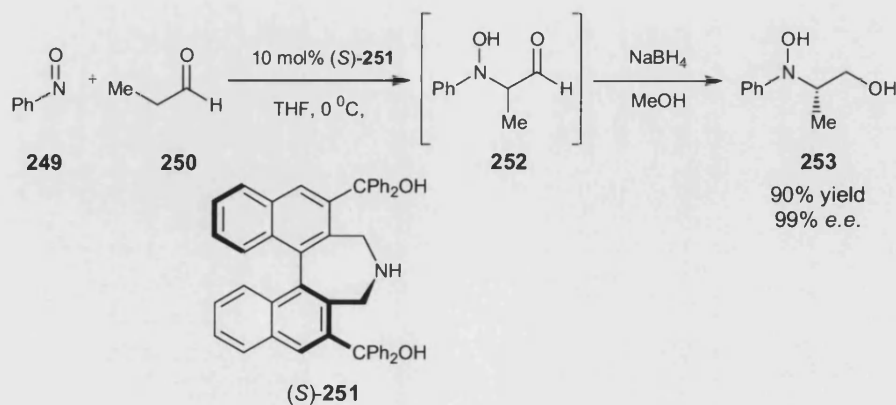
Scheme 93. Asymmetric organocatalytic epoxidation for the synthesis of natural product **245**

In 2005 MacMillan reported a new class of iminium catalysts capable of enantioselective cyclopropanations of α,β -unsaturated aldehydes by directed electrostatic activation.^[163] It was thought that zwitterions such as **247** derived from indole catalyst **246** would favour the formation of the (*Z*)-iminium species to minimise Van der Waals interactions between the substrate olefin and the aryl hydrogen. Consequently the carboxylate of the catalyst would direct ylide addition to the *Re* face of the electrostatically activated olefin to afford cyclopropanes such as **248**. This was found to be successful for a range of α,β -unsaturated aldehydes and ylides to afford cyclopropanes in reasonable yields (63 – 85%) and with high levels of enantioselectivity (89 – 96% *e.e.*) (see Scheme 94).

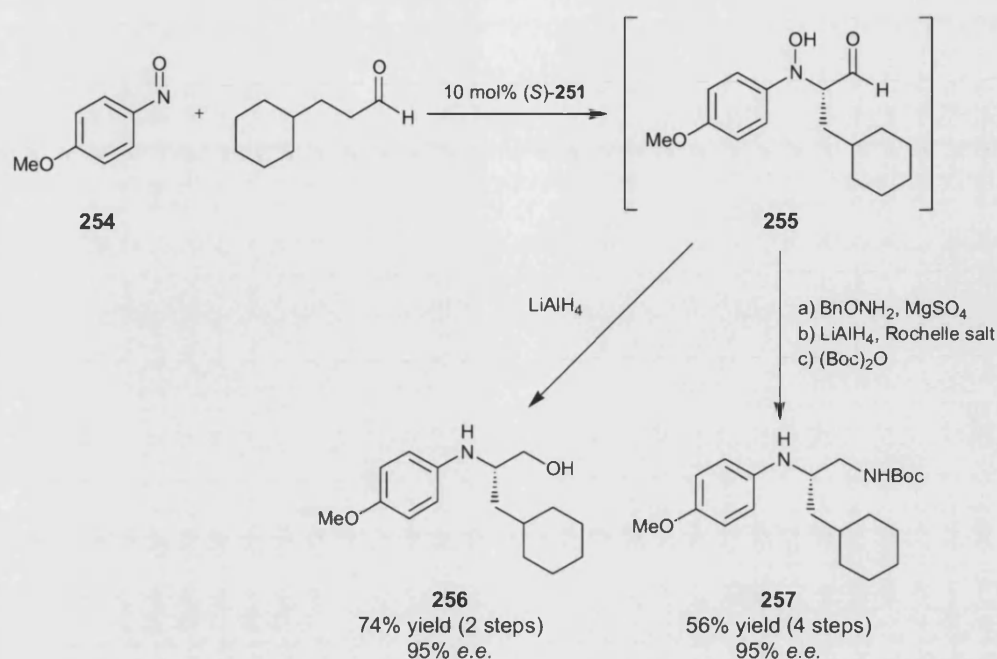


Scheme 94. Cyclopropanation of α,β -unsaturated aldehydes using a novel iminium catalyst

Recently Maruoka *et al.* have developed a novel axially chiral secondary amine catalyst **251** which was successful in affecting a direct asymmetric hydroxyamination of aldehydes **250** with nitrosobenzene **249**.^[164] This affords *N*-hydroxy- β -amino chiral aldehydes **252** which were reduced in situ with sodium borohydride to afford *N*-hydroxy- β -amino alcohols **253** in good isolated yield (70 – 90%) and excellent enantioselectivity (> 96% *e.e.*) (see Scheme 95). The reactions are carried out under very mild conditions in one hour and showed no evidence of the competing aminoxylation product. The synthetic utility of this reaction was extended by the use of *p*-methoxynitrosobenzene **254** in place of nitrosobenzene to yield chiral aldehyde **255** which can then be converted to either β -amino alcohol **256** or 1,2-diamine **257** in good yield and with no loss of enantioselectivity (see Scheme 96).

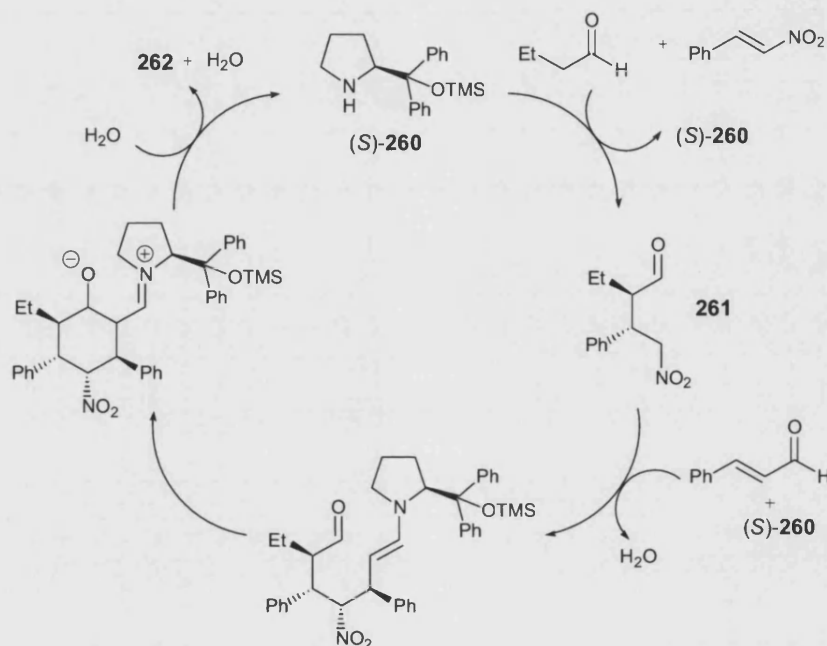
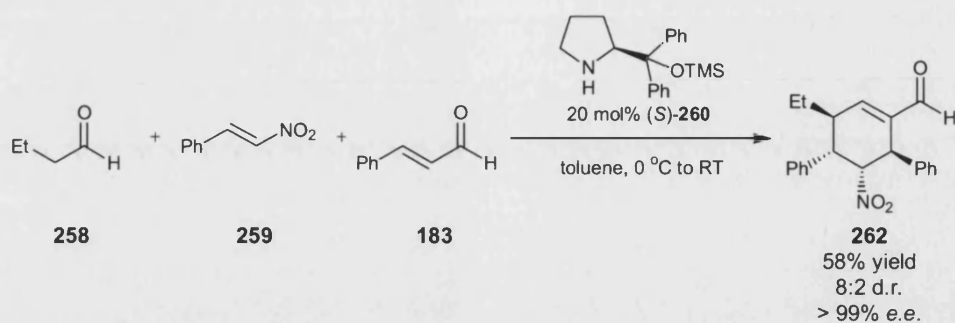


Scheme 95. Organocatalytic enantioselective hydroxyamination of aldehydes with nitrosobenzene



Scheme 96. One-pot synthesis of β -amino alcohol **256** and 1,2-diamine **257** catalysed by amine **251**

In 2006 Enders *et al.* reported an elegant synthesis of tetra-substituted cyclohexene carbaldehydes using a three component domino reaction catalysed by proline derivative **260**.^[165] This strategy involves a Michael/Michael/aldol condensation sequence to afford four new stereocentres with high diastereoselectivity and complete enantioselectivity (see Scheme 97). The reaction involves activation of linear aldehyde **258** by catalyst **260** by enamine formation, which then adds selectively to nitroalkene **259** in a Michael-type reaction. Subsequent hydrolysis liberates the catalyst which then forms an iminium ion with α,β -unsaturated aldehyde **183** which undergoes conjugate addition with the newly formed nitroalkane **261**. Intramolecular aldol condensation followed by hydrolysis releases the catalyst and the desired tetra-substituted cyclohexene carbaldehyde **262** with high levels of stereocontrol and moderate yield. This protocol was successfully employed for a range of substituents on the starting components and access to the opposite enantiomer of chiral cyclohexene carbaldehyde was simply achieved by using the alternative enantiomer of proline.



Scheme 97. Three component domino reaction for the synthesis of tetra-substituted cyclohexene carbaldehyde **262** catalysed by (S)-proline derivative **260**

1.3.12 Conclusions

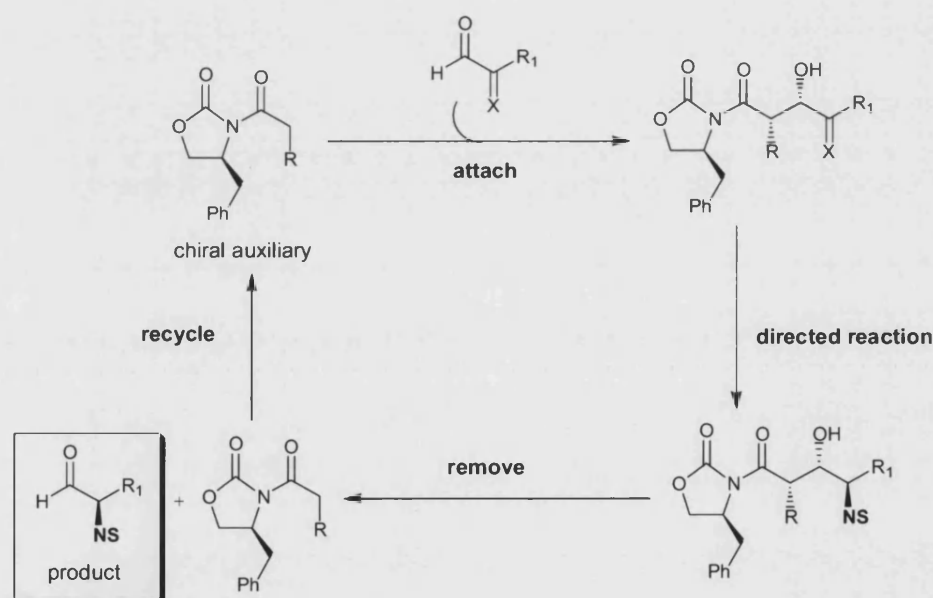
It can be seen that there are a variety of methods for the synthesis of chiral aldehydes. However, the structure of the desired aldehyde determines the choice of methodology used, with no “one fits all” approach. The remainder of this thesis will describe my investigations into using chiral auxiliaries and temporary stereocentres for the asymmetric synthesis of chiral aldehydes.

Chapter 2: A new strategy for the synthesis of chiral aldehydes

This chapter describes attempts to develop a novel aldol/ directed hydrogenation/ retro-aldol protocol for the asymmetric synthesis of chiral α -methyl aldehydes.

2.1 Introduction

A new three step procedure for the synthesis of α -substituted chiral aldehydes was proposed which relies on the relay of stereocontrol via the reversible formation of a temporary stereocentre (see Scheme 98).



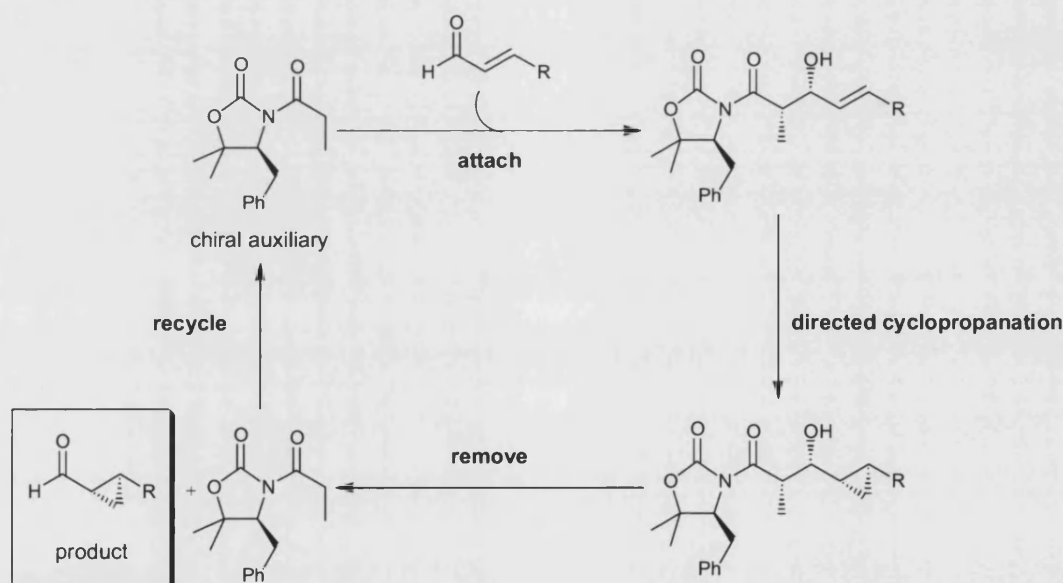
Scheme 98. A new strategy for the asymmetric synthesis of chiral aldehydes

In the first step the *N*-acylated oxazolidinone would act as a chiral auxiliary to control the stereoselectivity of its aldol reaction with an α,β -unsaturated aldehyde to produce a *syn*-aldol product. This *syn*-aldol contains a β -hydroxyl stereocentre that would then be used to direct the hydrogenation reaction of the alkene moiety generating a new stereocentre (NS). In the final step, the chiral α -substituted aldehyde would be cleaved via a retro-aldol

reaction, thus destroying the ‘temporary’ hydroxyl stereocentre and liberating the *N*-acylated oxazolidinone auxiliary for recycling. The overall outcome of this three step protocol would be the asymmetric hydrogenation of an α,β -unsaturated aldehyde to afford a chiral α -methyl aldehyde using the temporary β -hydroxyl stereocentre of an aldol intermediate to relay stereochemistry from the chiral auxiliary fragment to the remote alkene functionality.

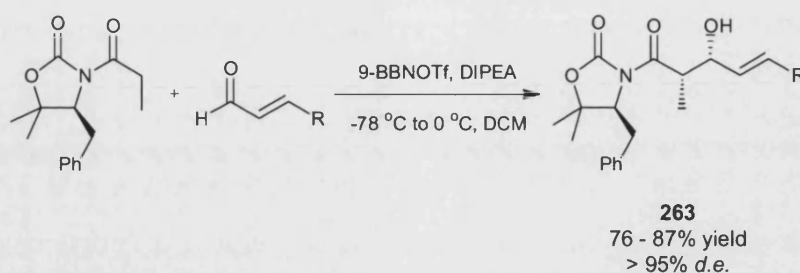
2.1.1 Previous efforts to develop the three-step strategy

Research carried out by another member of the SDB group during the course of my PhD. had shown this ‘temporary stereocentre’ strategy to be a viable approach for the asymmetric synthesis of a range of chiral cyclopropane carboxaldehydes as shown in Scheme 99.^[166]



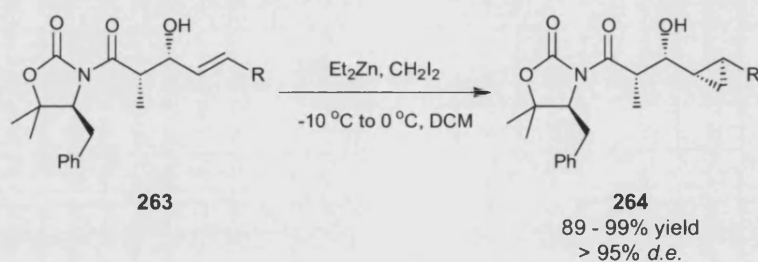
Scheme 99. Synthesis of chiral cyclopropane carboxaldehydes using a novel three-step strategy

In step one, a stereoselective boron enolate mediated aldol reaction was used to synthesise unsaturated *syn*-aldol product **263** which contained a β -hydroxyl stereocentre in greater than 95% diastereomeric excess (see Scheme 100).



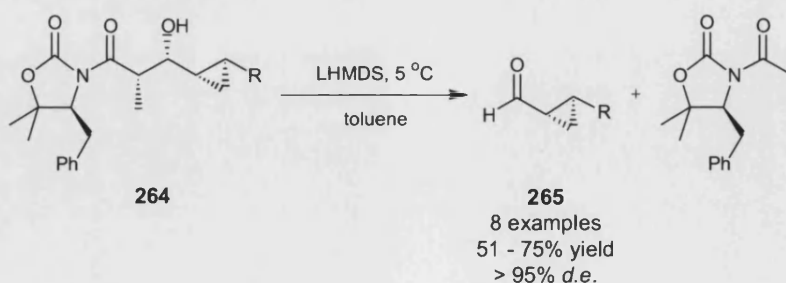
Scheme 100. Synthesis of unsaturated aldol product **263**

The new β -hydroxyl stereocentre was then used to control a β -hydroxyl-directed diastereoselective cyclopropanation reaction using diethyl zinc and iodomethane to generate cyclopropane aldol **264** in greater than 95% diastereoselectivity (see Scheme 101).



Scheme 101. Highly diastereoselective β -hydroxyl-directed cyclopropanation reaction

Finally carrying out an anionic retro-aldol reaction on cyclopropane aldol **264** resulted in cleavage to afford enantiopure cyclopropane carboxaldehyde **265** and the *N*-propionyl-oxazolidin-2-one in good yield and excellent diastereoselectivity (see Scheme 102).

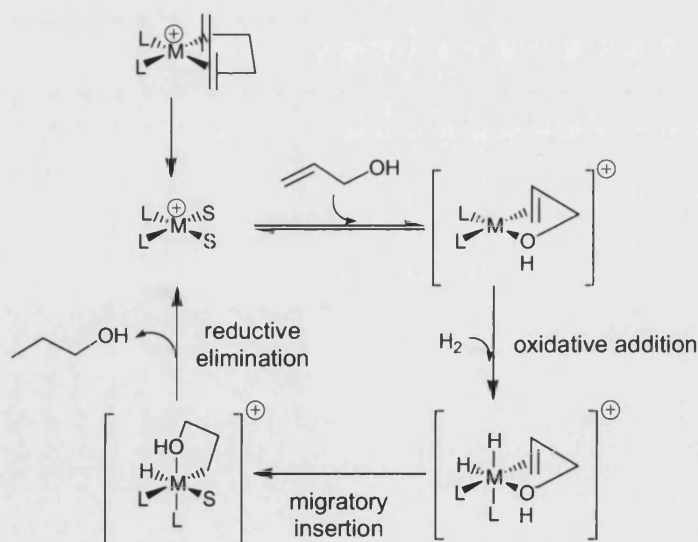


Scheme 102. Retro-aldol reaction to yield chiral cyclopropane carboxaldehydes **265**

This work demonstrated that this novel strategy for relaying chirality could be successfully applied to the synthesis of chiral cyclopropane carboxaldehydes using a directed cyclopropanation reaction, and as a consequence it was decided to investigate whether this protocol could be extended to other substrate-directed reactions for the asymmetric synthesis of other classes of chiral aldehyde.

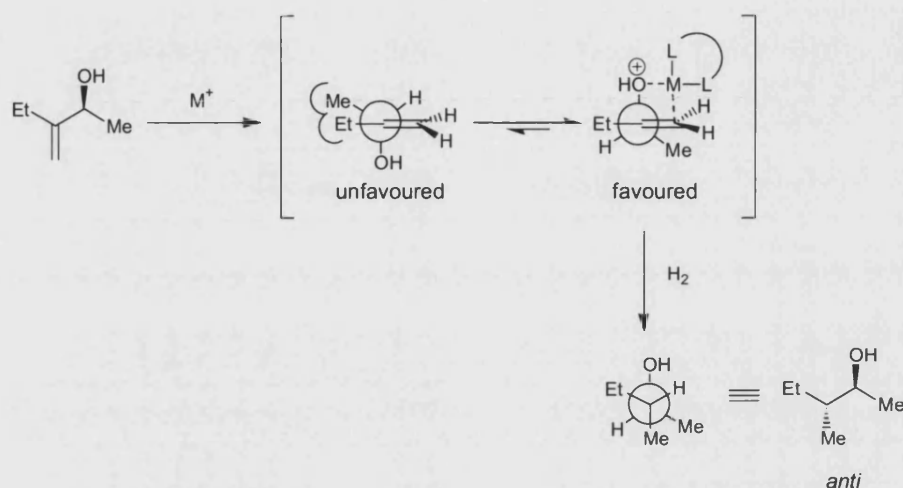
2.2 Hydroxyl-directed hydrogenation

Directed hydrogenation reactions of allylic alcohols are an important class of substrate-directed reaction. Both homogeneous and heterogeneous catalysts have shown to be effective in this transformation, however homogeneous methods are generally considered to exhibit higher levels of selectivity under milder conditions.^[167] The reaction requires a hydroxyl-group in close proximity to the alkene which can bind to the metal centre and thereby control delivery of hydrogen from the metal complex to the double bond.^[168] In the homogeneous reaction stereocontrol occurs because the metal centre is simultaneously coordinated to the directing group, the alkene and hydrogen in the transition state of the reaction (see Scheme 103).



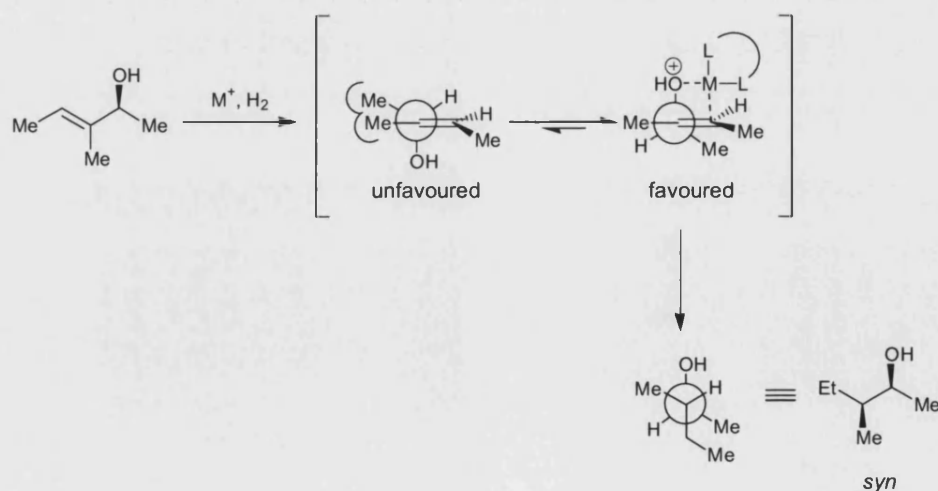
Scheme 103. Catalytic cycle proposed for homogeneous hydroxyl-directed hydrogenation reactions

In cyclic systems the hydrogen is delivered to the same face as the hydroxyl-group and in acyclic systems the stereochemistry is governed by allylic strain. For a 1,1-substituted alkene minimisation of allylic $A^{(1,2)}$ -strain dominates and therefore generally favours formation of the *anti* isomer of product as shown in Scheme 104.^[169]



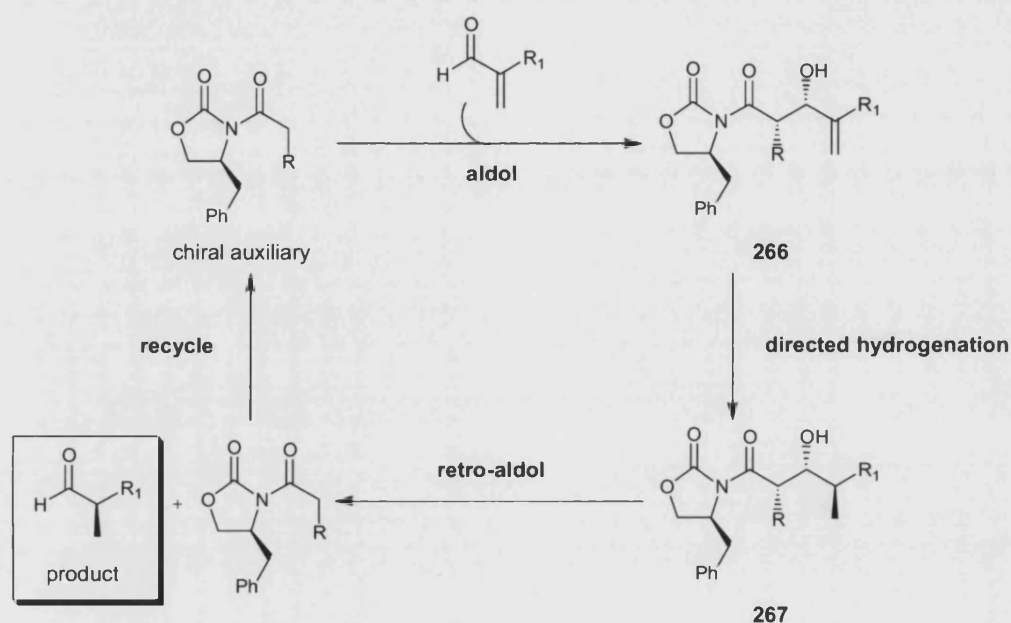
Scheme 104. Minimisation of allylic strain in the transition state of directed hydrogenation of a 1,1-substituted alkene

In the case of a 1,2-substituted alkene the opposite *syn*- isomer is formed, which is also predicted from minimisation of allylic strain arguments (see Scheme 105).



Scheme 105. Minimisation of allylic strain in the transition state of directed hydrogenation of a 1,2-substituted alkene

It was proposed that the alcohol functionality of β -hydroxy-*N*-acyl-oxazolidin-2-ones **266** might prove effective in controlling homogeneous directed-hydrogenation reactions of their alkene functionality, which after retro-aldol cleavage of the resultant hydrogenated aldol product **267** would afford a route to enantiopure α -methyl aldehydes (see Scheme 106).



Scheme 106. Proposed synthesis of chiral α -methyl aldehydes via a novel three-step strategy

2.3 Directed hydrogenation reactions of related aldol substrates

A review of the literature revealed that there was some precedent that directed hydrogenation of this class of aldol substrate might proceed with good diastereocontrol.

In 1984 Evans *et al.* reported investigations into directed hydrogenations of related aldol structures **268** and **269**.^[170] They used two different metal catalysts, Crabtree's iridium catalyst $\text{Ir}(\text{COD})(\text{py})(\text{PCy}_3)\text{PF}_6$ which had previously been shown to be effective in hydroxyl-directed hydrogenation of cyclic and homoallylic alcohols,^[171,172] and the

rhodium catalyst $[\text{Rh}(\text{NBD})(\text{DIPHOS-4})]\text{BF}_4$ which had also been shown to be effective for hydrogenation of acyclic allylic alcohols (see Figure 3).^[173]

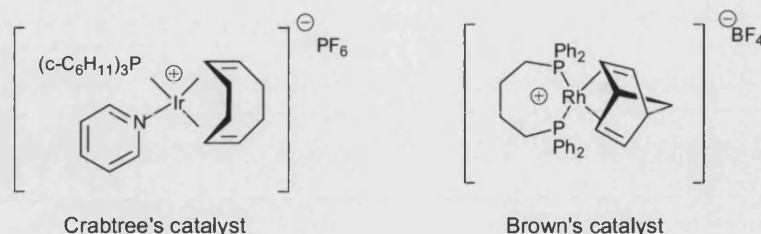
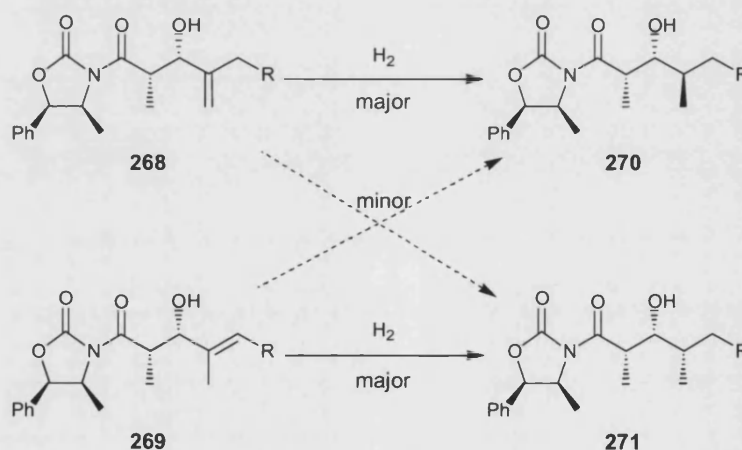


Figure 3. Structures of catalysts used for the directed hydrogenation of aldols **268** and **269**

According to the allylic strain models previously described, it would be expected that allylic alcohols **268** and **269** would afford two diastereomeric products **270** and **271** as shown in Scheme 107.



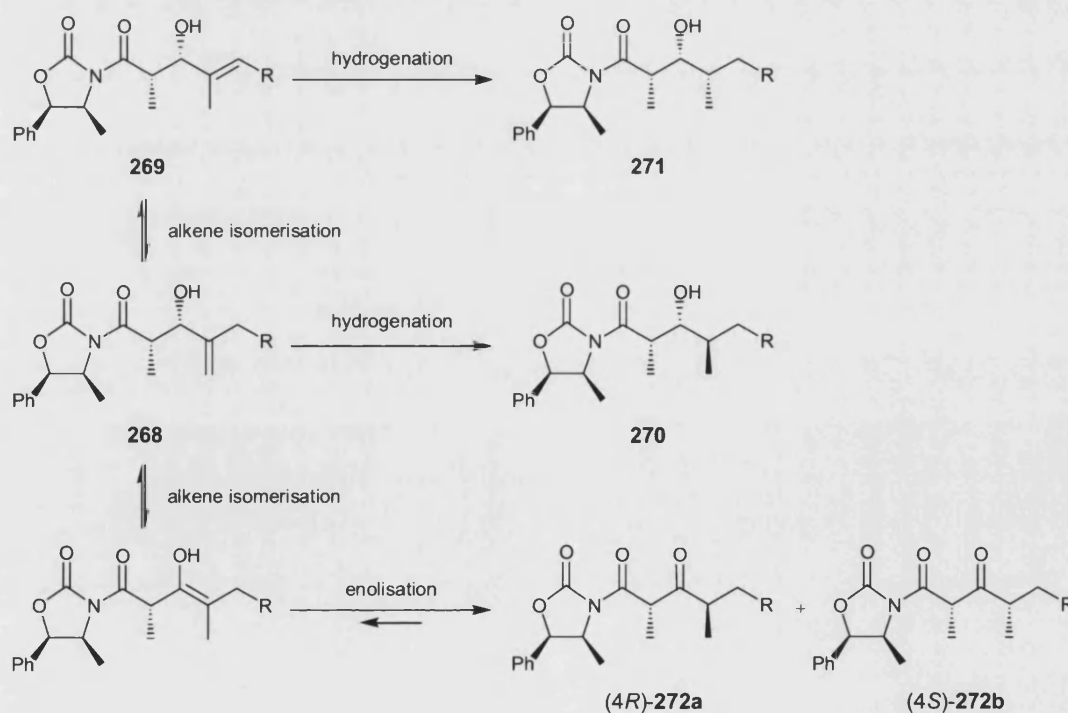
Scheme 107. Expected products from stereoselective directed hydrogenation reaction of *syn*-aldols **268** and **269**

Surprisingly, at atmospheric pressure both catalysts showed little diastereoselection (see Table 2.1), with large amounts of unwanted β -keto imide product **272** being formed from isomerisation of the alkene functionality, followed by enol tautomerisation (see Scheme 108). At more elevated pressures (640 psi) the rhodium catalyst showed improved diastereoselectivity (see Table 2.1), however reactions using the iridium catalyst were still poor. It was thought that at low pressures the rate of hydrogenation and alkene

isomerisation were comparable leading to poor diastereoselectivity due to competing hydrogenation reactions of both **268** and **269**. In the case of the rhodium catalyst it was suggested that the rate determining step was dependent on hydrogen pressure; at low pressures oxidative addition of hydrogen to the catalyst-substrate complex was rate determining, whilst at higher pressures the complexation step of substrate and catalyst becomes rate determining.

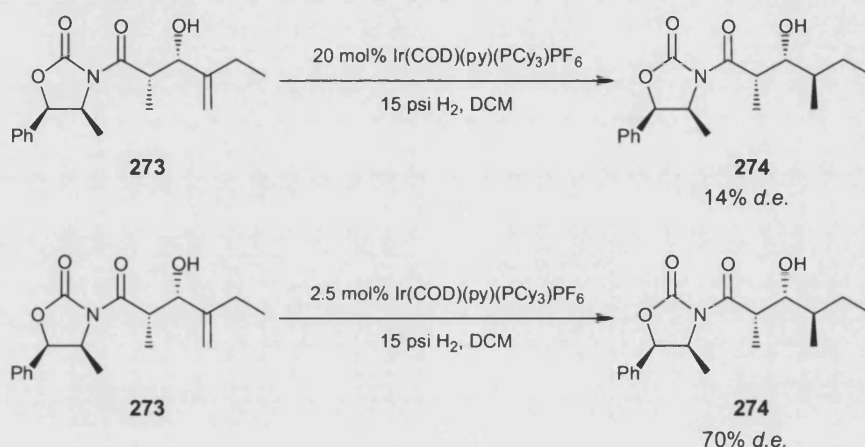
Substrate	Ratio 270:271 at 15 psi H ₂		Ratio 270:271 at 640 psi H ₂
	Ir	Rh	
268 , R = Me	51:49	25:75	93:7
269 , R = Me	56:44	13:87	9:91
268 , R = Ph	54:46	71:29	93:7
269 , R = Ph	60:40	21:79	6:94
268 , R = ^t Pr	47:53	52:48	94:6
269 , R = ^t Pr	54:46	12:88	8:92

Table 2.1 Directed-hydrogenation reaction of *syn*-aldols **268** and **269** with iridium and rhodium catalysts^[170]



Scheme 108. Isomerisation/enolisation mechanism for the formation of ketone **272**

These initial hydrogenation reactions were carried out using 17.5 mol% catalyst loading, however, in a later study it was found that the diastereoselectivity of the iridium catalysed reaction could be increased by reducing the catalyst loading.^[174] For example, hydrogenation of **273** with 20 mol% of catalyst gave a 14% diastereomeric excess of in favour of aldol **274**, whereas reducing the catalyst loading to 2.5 mol% increased the diastereomeric excess to 70% (see Scheme 109).



Scheme 109. Effect of catalyst loading on the diastereoselectivity of iridium catalysed hydrogenation reactions of **273**

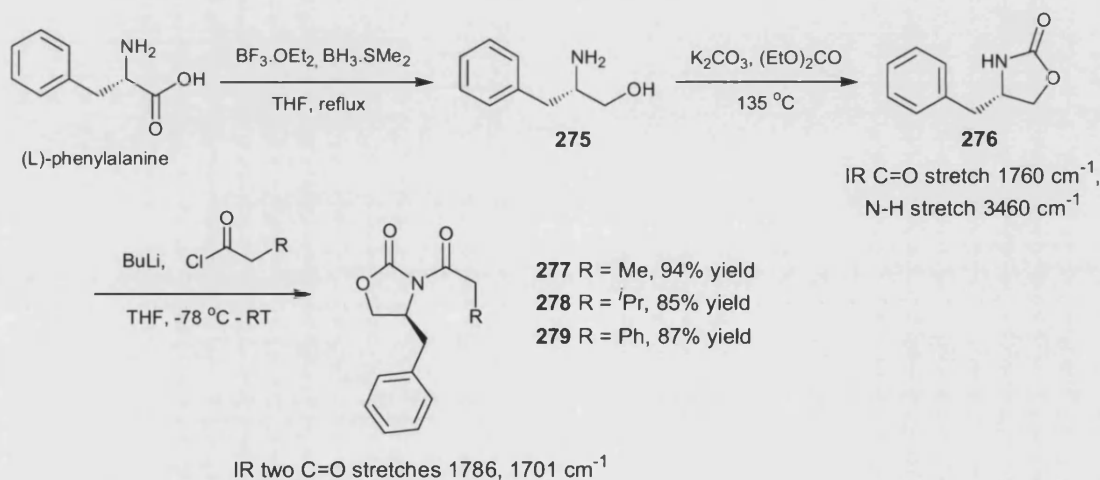
In this case the diastereoselectivity was found to be independent of the hydrogen pressure but was found to be highly substrate dependent. The authors suggested that this meant that isomerisation between the starting materials **268** and **269**, which would reduce the selectivity of the directed hydrogenation reaction, was not the cause of the low levels of diastereoselectivity observed with this catalyst. Iridium complexes are known to aggregate in solution and consequently it was proposed that at high catalyst loading there might be more than one catalytic species operating.

These results by demonstrated a clear literature precedent that directed hydrogenation reactions might prove applicable to our ‘temporary stereocentre’ strategy for the asymmetric synthesis of chiral aldehydes, and therefore my first goal was to develop an effective and diastereoselective directed hydrogenation protocol for this class of *syn*-aldol substrate.

2.4 Synthesis of Evans' oxazolidin-2-one

At the start of my PhD, elimination problems associated with the retro-aldol reaction of β -hydroxy *N*-acyl-oxazolidin-2-ones had not been established (*vide supra*) and as a consequence I initially targeted *syn*-aldol products derived from conventional Evans' oxazolidin-2-ones.

According to Evans' original procedure, (*S*)-4-benzyl-oxazolidinone **276** was synthesised in good yield by borane reduction of L-phenylalanine followed by cyclisation of the resulting amino alcohol **275** with diethyl carbonate under basic conditions.^[175] Deprotonation with *n*-butyl lithium and addition of an acid chloride afforded *N*-acylated oxazolidin-2-ones **277** – **279** in good yield. The products could be crystallised as described in the literature, however it was found that better isolated yields were obtained using column chromatography for purification (see Scheme 110).



Scheme 110. Synthesis of *N*-acylated Evans' oxazolidin-2-ones **277** – **279**

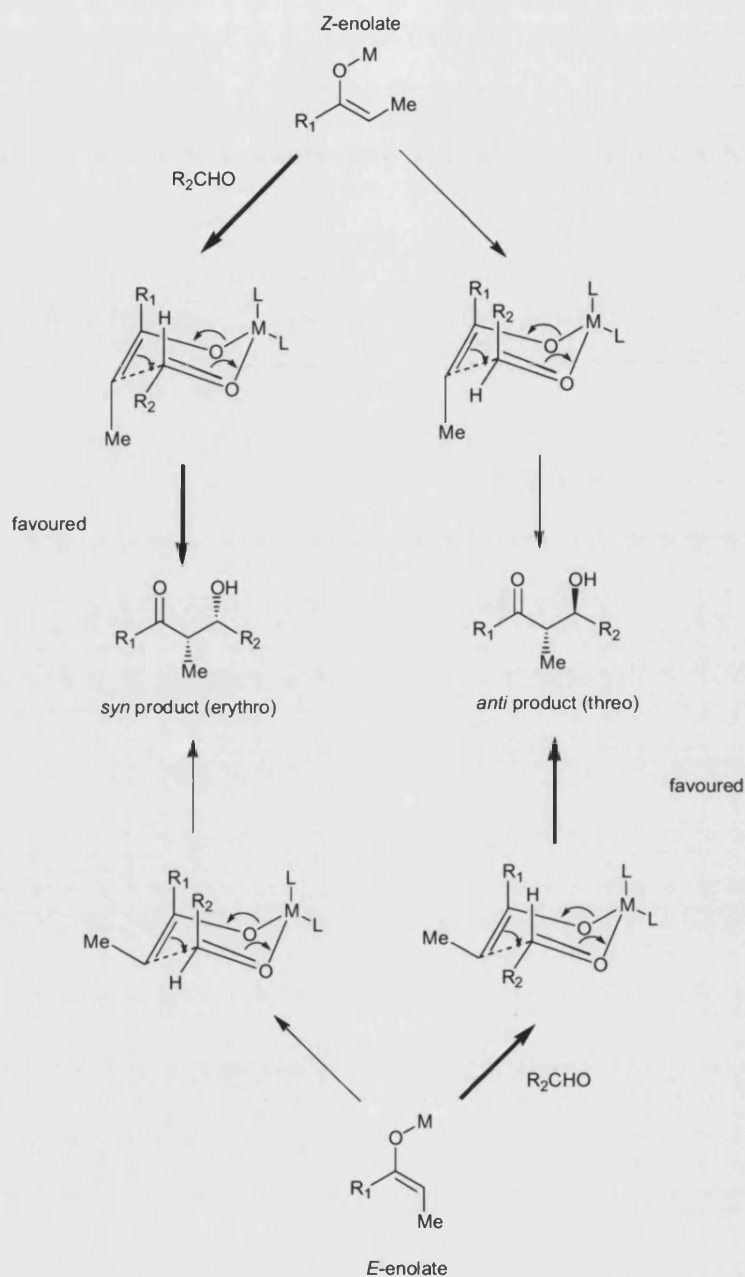
2.5 Development of the *syn*-aldol reaction

My next goal was to develop diastereoselective methodology for the asymmetric synthesis of *syn*-aldols with high diastereomeric excess.

2.5.1 Overview of the asymmetric aldol reaction

The addition of an enolizable carbonyl compound to an aldehyde or ketone is known as the aldol reaction and is a classical reaction in organic synthesis. It allows for the formation of a new carbon-carbon bond with the simultaneous generation of two new stereocentres. The aldol fragment is a common motif in many natural products and therefore it has become a very widely used transformation.^[176]

In the 1950's Zimmerman and Traxler accounted for diastereoselection in the aldol reaction by suggesting that the reaction proceeds via a chair-like transition state involving coordination of the metal ion to both the enolate and carbonyl substrates, as shown in Scheme 111.^[177]



Scheme 111. Zimmerman–Traxler model accounting for diastereoselectivity of aldol reactions

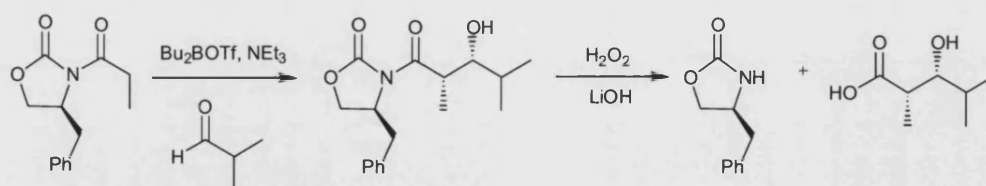
The favoured conformation minimises steric interactions between the R_1 -alkyl group of the enolate and the R_2 -substituent of the carbonyl substrate. This is supported by evidence that for lithium enolates, diastereoselection increases as the steric bulk of the R_1 group increases ($tBu > iPr > Et > OMe > H$).^[178] In the case of the (*Z*)-enolate, placing the large R_2 group in the equatorial position rather than the axial position minimises 1,3-diaxial interactions within the six-membered transition state and therefore favours formation of the

syn-aldol via the lower energy transition state. With the (*E*)-enolate the opposite selectivity occurs with the low energy transition state generally favouring formation of the *anti*-aldol, by minimisation of 1,3-diaxial interactions between R₁ and R₂.

In order for the aldol transformation to be viable for the formation of chiral products it is necessary to be able to control the absolute stereochemistry of the aldol product as well as the diastereoselection. There are three common strategies for achieving this; Mukaiyama-type catalytic aldol reaction using masked silyl-enolates, direct catalytic aldol additions using transition metal catalysts or organocatalysts, and chiral auxiliary-based aldol reactions.^[179] Although the use of chiral auxiliaries introduces additional steps into a synthesis involving attachment and removal of the auxiliary, they often overcome many of the difficulties of using catalysts by enabling diastereomeric aldol products to be purified to homogeneity. Furthermore, many chiral auxiliaries are cheap and easy to make and can be readily recycled with their reactions generally proceeding under relatively mild conditions without the need for large excesses of reagents. Carrying out stereoselective aldol reactions using Evans' oxazolidinone auxiliary was key to our chiral relay strategy, and therefore the scope and limitations of this area are now discussed briefly.

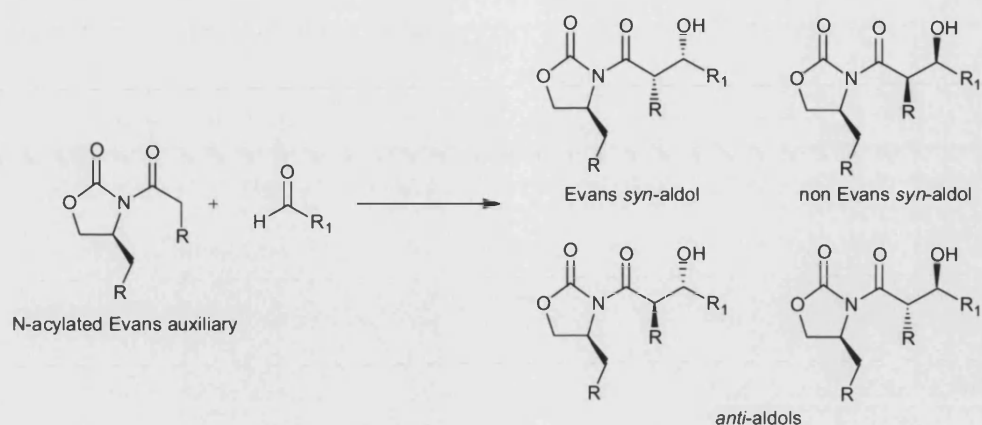
2.5.2 Evans' auxiliary mediated aldol reactions

The *N*-acylated Evans' oxazolidin-2-one has been widely used as an effective auxiliary for the asymmetric aldol reaction, and is known to react with a range of aldehydes in good yield and with high diastereoselectivity (see Scheme 112).^[175]



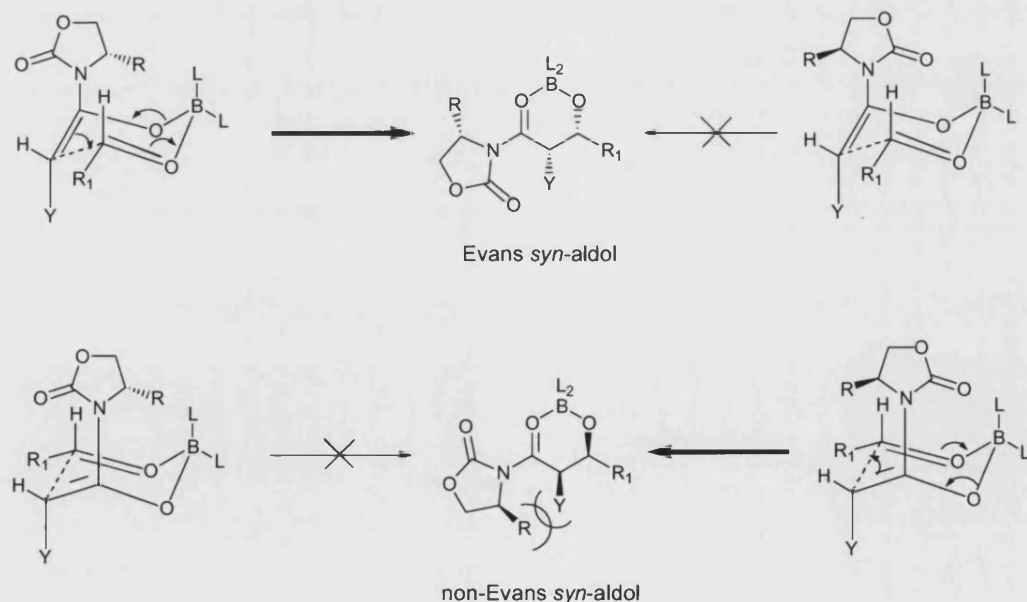
Scheme 112. *Syn*-aldol reactions of boron-enolates of *N*-acyl-oxazolidin-2-ones

There are four possible diastereoisomers that may be formed in the aldol reaction of *N*-acyl-oxazolidin-2-ones, as shown in Scheme 113.



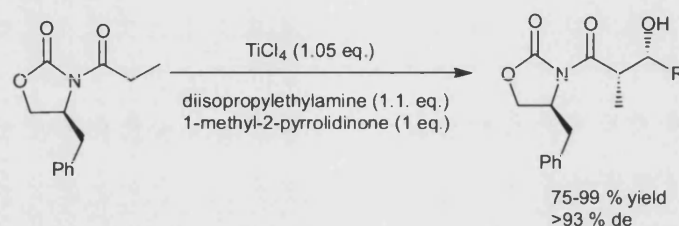
Scheme 113. Possible diastereoisomers formed during the asymmetric aldol reaction

The classic (*Z*)-boron enolate derived aldol reaction favours the Evans *syn*-aldol through formation of a Zimmerman-Traxler type chair transition state, as shown in Scheme 114.^[180] In order to observe high selectivity an α -substituent (Y) must be present, with the aldehyde substrate being directed away from the alkyl group of the chiral auxiliary fragment to favour an Evans *syn*-aldol product. However, competing formation of the non-Evans *syn*-aldol can occur if the Y substituent of the enolate is hydrogen, leading to poor diastereocontrol.



Scheme 114. Formation of Evans' *syn*-aldol via chair-like transition state

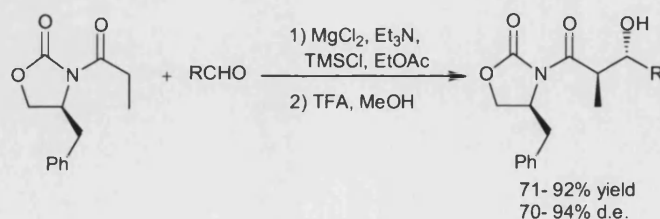
The use of sterically demanding metal centres greatly improves stereocontrol in the aldol reaction. For dialkylboron enolates the stereochemistry of the *syn*-aldol product is controlled by the stereochemistry of the (*Z*)-enolate formed, whereas for dicyclopentadienylchlorozirconium enolates, *syn*-aldol products have been observed arising from either (*E*)- or (*Z*)-enolate geometry.^[181] Recent reports using chlorotitanium enolates have also been shown to give very good yields and selectivity for the Evans *syn*-product, as shown in Scheme 115.^[182]



Scheme 115. Evans' asymmetric *syn*-aldol reaction using chlorotitanium enolates

Chelation control has also been reported for other metals including, lithium, zinc and tin although levels of diastereoselectivity are generally inferior to boron enolates.^[183] However, boron enolates in the presence of excess Lewis acids such as diethylaluminium chloride, have been reported to give access to *anti*-aldol products, however attempts to reproduce this chemistry in the SDB group have so far proven unsuccessful.^[180,184]

More recently, Evans has reported the use of magnesium chloride, in the presence of triethylamine and chlorotrimethylsilane, to catalyse *anti*-aldol reactions with a range of aromatic and unsaturated aldehydes in good yields and moderate-to-high diastereoselectivity (see Scheme 116).^[185]

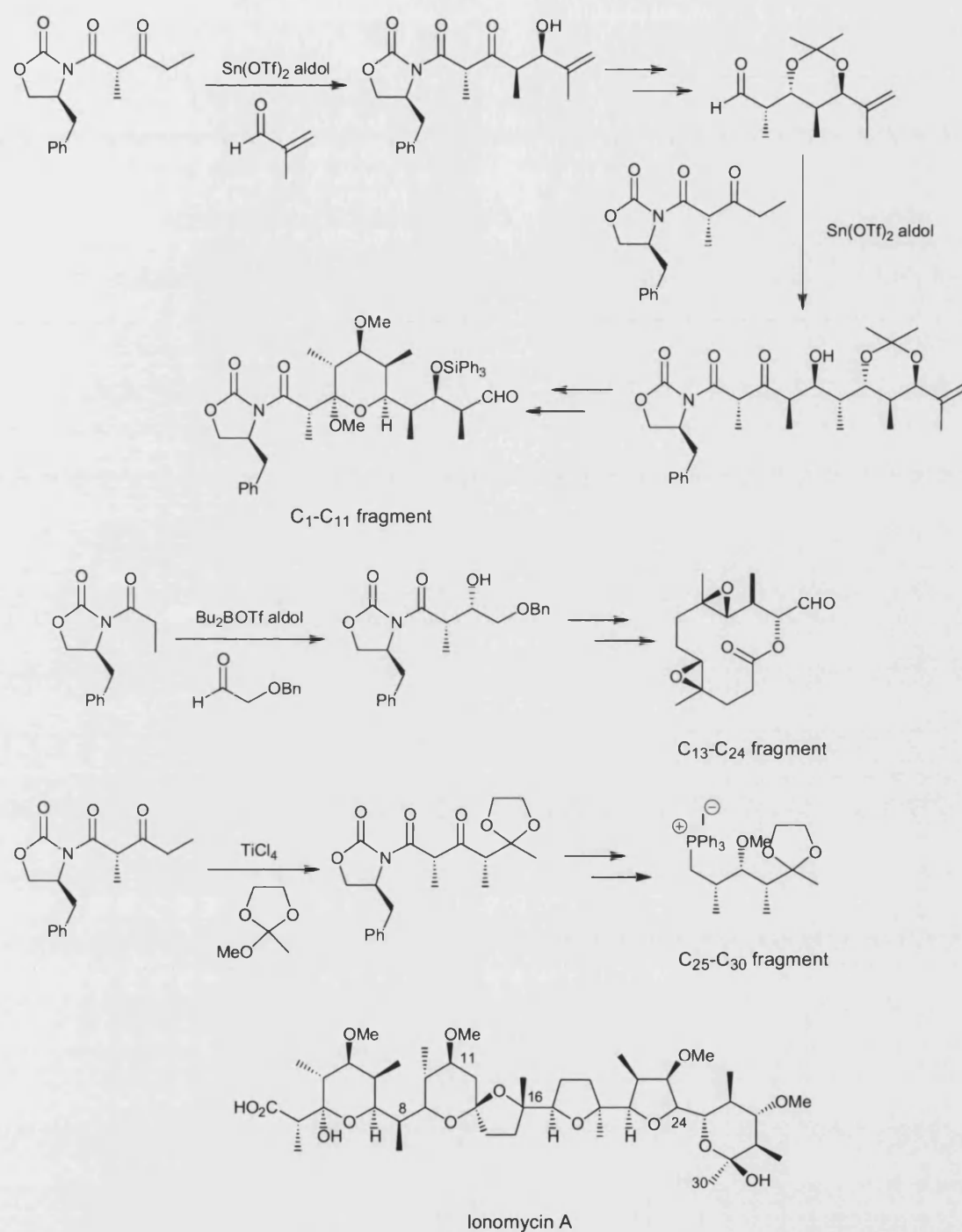


Scheme 116. Magnesium chloride catalysed *anti*-aldol reactions

This method was shown to be applicable to a range of aldehydes, although the addition of NaSbF₆ (30 mol %), or an increase in catalyst loading (up to 20 mol %), was necessary for *anti*-aldol reactions of less reactive aldehydes.

Several studies have shown that these types of aldol reactions can be capricious, with levels of stereocontrol being dependent on the choice of solvent and base used for deprotonation. For example, it has been shown for titanium enolates that using diethyl ether as a solvent results in a 5-fold increase in diastereoselectivity compared to THF,^[186] with suggestions that this was due to the ability of THF to bind to the titanium counterion, thus disrupting the Zimmerman-Traxler transition state. Alternatively, it has been shown that using triethylamine as a base to generate boron enolates gives superior diastereoselection to isopropylethylamine,^[187] which may be due to the resulting ammonium salt being involved in the transition state.

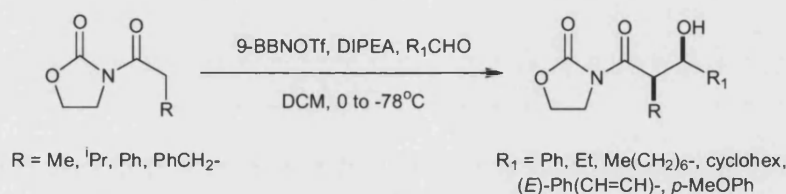
The power of the Evans aldol reaction for stereoselective synthesis is readily demonstrated by considering the number of times it has been used in natural product synthesis. For example, Evans *et al.* reported the synthesis of the polyether antibiotic lonomycin A using a range of auxiliary based aldol and acylation reactions to control the absolute stereochemistry of all the major fragments used to assemble the natural product (see Scheme 117).^[188]



Scheme 117. Use of a range of aldol reactions to control the configuration of the major fragments used in the asymmetric synthesis of Ionomycin A

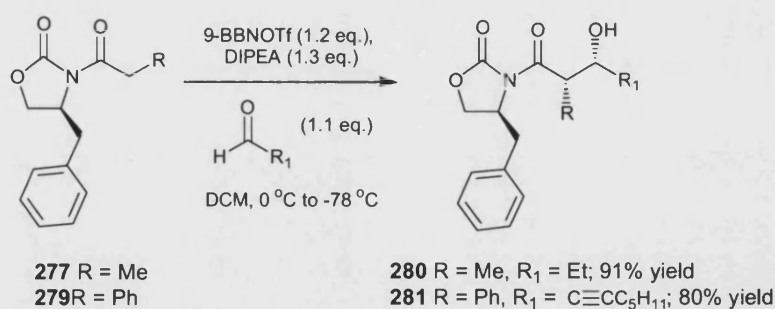
2.5.3 Optimisation of the aldol reaction

As described in the previous section, a number of protocols had been reported in the literature for the asymmetric aldol reactions of *N*-acylated oxazolidinones.^[175,182-187,189] Previous work within the group had shown that the use of 9-BBNOTf with diisopropylethylamine was an effective method for the synthesis of the *syn*-aldol product of racemic *N*-acylated oxazolidinones (see Scheme 118).^[190]



Scheme 118. Synthesis of *syn*-aldol products using racemic *N*-acylated oxazolidinones

These conditions were therefore used to optimise the *syn*-aldol reactions of *N*-acyl oxazolidin-2-ones **277** and **279** (see Scheme 119). Therefore, 1.1 equivalents of 9-BBNOTf was added to the corresponding *N*-acyl-oxazolidin-2-ones at 0 °C in dichloromethane, with 1.3 equivalents of diisopropylethylamine added after 30 minutes. After a further 30 minutes the reaction was cooled to -78 °C before addition of the appropriate aldehyde, which gave the corresponding *syn*-aldols **280** – **281** in excellent yield after purification by chromatography.



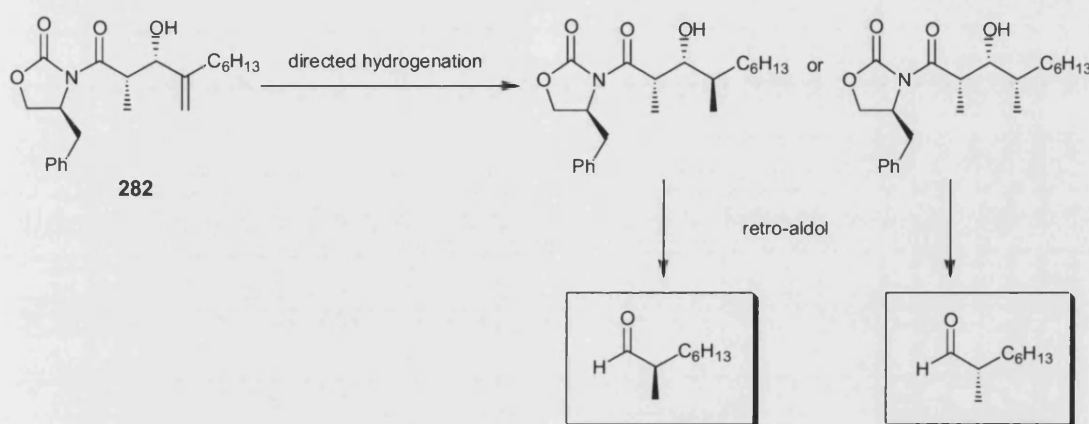
Scheme 119. Model *syn*-aldol reactions

¹H NMR spectroscopic analysis showed selective formation of only one diastereomer which was assigned as the *syn*-aldol by comparison with literature data,^[175] and

consideration of the coupling constant between their α - and β -protons that was between 5 – 7 Hz, with *anti*-aldols known to exhibit where coupling constants greater than 8.0 Hz.^[185]

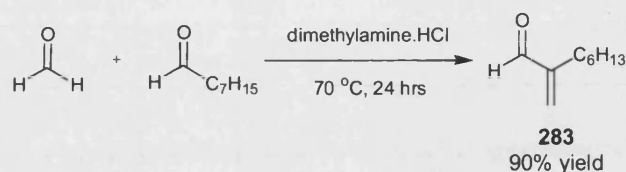
2.5.4 Synthesis of unsaturated aldols

Recapping, our directed hydrogenation strategy required *syn*-aldol substrates which contained a γ -alkene functionality, such as **282**, whose hydrogenated products would then undergo retro-aldol reaction to afford chiral α -methyl aldehydes as shown in Scheme 120.

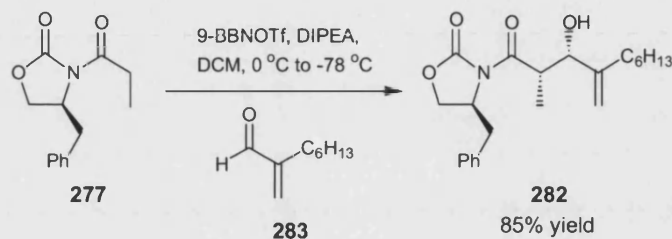


Scheme 120. Synthesis of chiral aldehydes containing an α -methyl stereocentre

The α -methylene aldehyde **283** required to prepare *syn*-aldol **282** was therefore synthesised according to the procedure previously described by Marvel *et al.*^[191] An aldehyde containing a C_6 alkane chain was chosen for ease of handling because it had a high enough boiling point to enable common solvents to be removed *in vacuo*, but was volatile enough to allow purification by distillation as required. Therefore, octanal, dimethylamine hydrogen chloride and formaldehyde (37% solution in water) were mixed together and left to reflux overnight to yield aldehyde **283** in good yield and purity, with no evidence of any aldehyde products arising from isomerisation of the alkene functionality (see Scheme 121). This α -methylene aldehyde **283** was then reacted without further purification with the boron enolate of *N*-acylated auxiliary **277** to yield *syn*-aldol product **282** according to our optimised procedure in good yield and diastereoselectivity (see Scheme 122).



Scheme 121. Synthesis of α,β -unsaturated aldehyde **283**



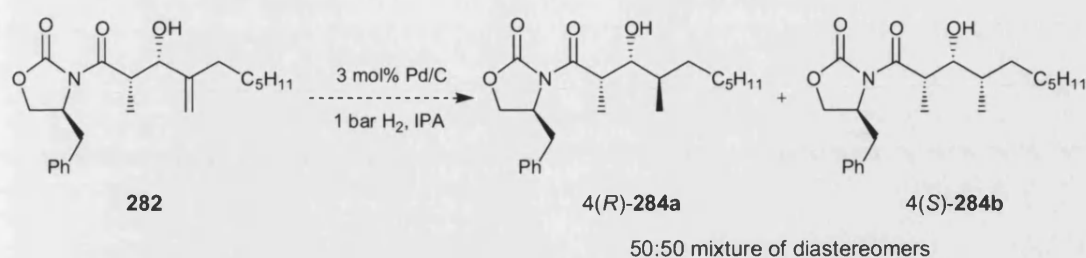
Scheme 122. Synthesis of γ -unsaturated *syn*-aldol **282**

With γ -unsaturated *syn*-aldol **282** in hand, it was then employed as a substrate to screen a series of directed hydrogenation reactions using different transition metal catalysts.

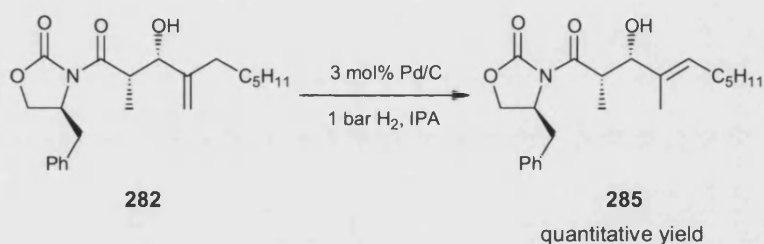
2.6 Directed hydrogenation reactions

2.6.1 An unexpected reaction

Prior to carrying out screening of catalysts in our substrate-directable reactions, aldol **282** was first subjected to a hydrogenation reaction with Pd/C with the intention of preparing an authentic 50:50 mixture of diastereomers (4*R*)-**284a** and (4*S*)-**284b** which could then be used to confirm the diastereomeric excess of our directed hydrogenation reactions (see Scheme 123). Unexpectedly, instead of forming the reduced products (4*R*)-**284a** and (4*S*)-**284b**, this reaction lead to a quantitative yield of the isomerised starting material **285** in 3 hours, which showed a characteristic alkene triplet resonance at δ 5.50 ppm in its ^1H NMR spectrum (see Scheme 124).



Scheme 123. Expected non-diastereoselective hydrogenation reaction of aldol **282** using Pd/C as a catalyst



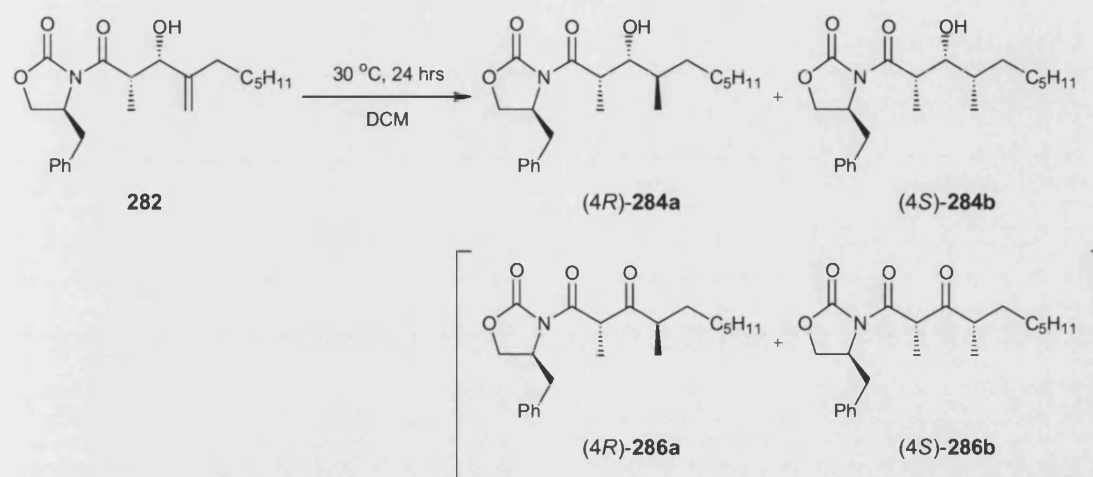
Scheme 124. Observed alkene isomerisation reaction of aldol **282** using Pd/C as a catalyst

Investigations into the mechanism of this remarkable isomerisation reaction are discussed later in this thesis. However, I was delighted by the outcome of this isomerisation reaction since it provided an easy route to the synthesis of unsaturated aldol **285** as an alternative substrate for our hydrogenation reactions, which meant we did not have to prepare it separately via *syn*-aldol reaction of its parent aldehyde.

2.6.2 Initial catalyst screening reactions

As described earlier, previous work by Evans *et al.* using analogous substrates had shown that γ -unsaturated aldols such as **268** could be hydrogenated with Brown's or Crabtree's catalyst in moderate to good diastereoselectivity depending on the conditions used.^[170,174] Therefore our *syn*-aldol product **282** was subjected to a screen of hydrogenation reactions using Evans' original hydrogenation conditions as a starting point for our investigations. Crabtree's iridium catalyst Ir(COD)(py)(PCy₃)PF₆ and the rhodium catalyst [Rh(NBD)(DIPHOS-5)]PF₆ developed by Brown were screened as catalysts for hydrogenation of unsaturated aldols **282** and **285**. Evans *et al.* had previously used the DIPHOS-4 variant of this rhodium catalyst, however we chose the commercially available DIPHOS-5 variant which had also been shown to be effective for the homogeneous

hydrogenation of allylic alcohols.^[169,173] Trial reactions were carried out using Evans' original conditions on *syn*-aldol **282** at both 2.5 mol% and 17.5 mol% catalyst loading and at 1 bar and 4.5 bar H₂ pressure, the results of which are summarised in Table 2.2.

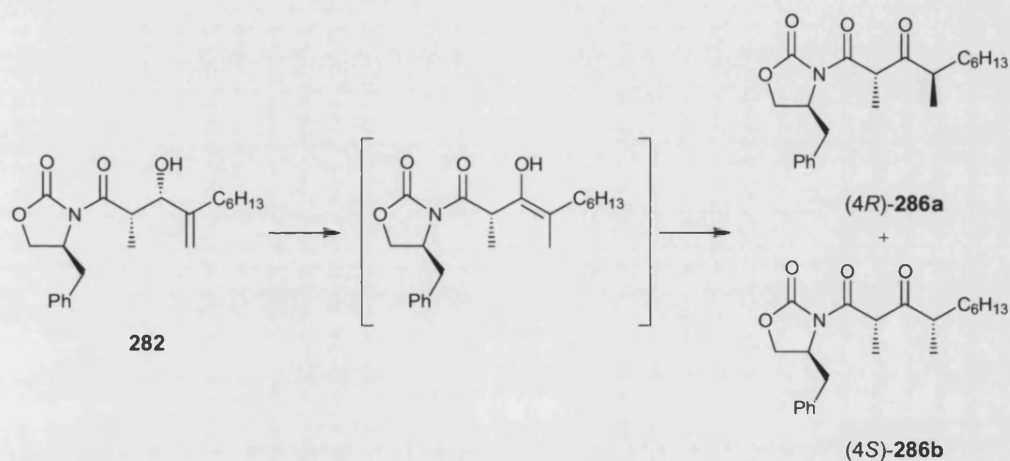


Catalyst	Loading (mol%)	Pressure	
		1 bar	4.5 bar
 Crabtree's	2.5	70% SM 282	SM 282
	17.5	90% ketone 286	50:50 ketone 286 : product 284
 Brown's	2.5	65% ketone 286	50% SM 282
	17.5	100% product 284 (mixture of diastereomers)	100% product 284 (mixture of diastereomers)

Table 2.2 Summary of results of initial hydrogenation screen on γ -unsaturated aldol **282**

Although Evans had reported good results using Crabtree's iridium catalyst at low catalyst loading, in our hands these hydrogenation reactions proved unsatisfactory. At higher catalyst loadings the starting aldol isomerised to give ketone product **286** at low pressure

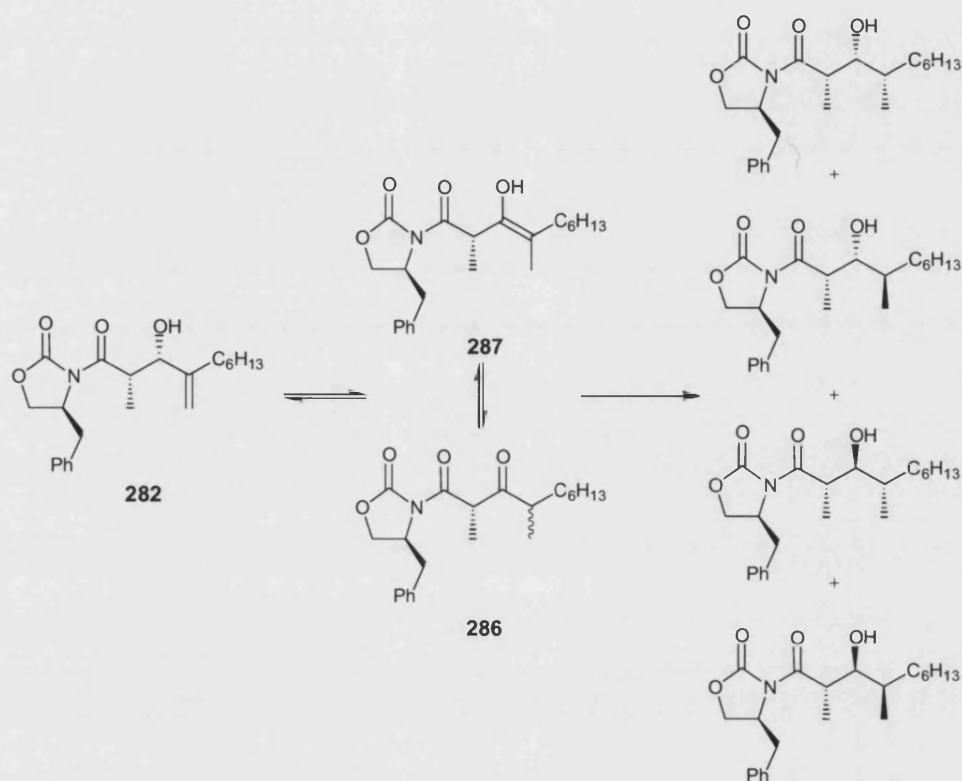
(see Scheme 125), whereas higher pressure gave a mixture of starting material **282** and ketone **286**. The mixture of diastereomeric ketones (4*R*)-**286a** and (4*S*)-**286b** was evident from the presence of a multiplet (two sets of overlapping quartets for the two diastereomers) at 4.84 ppm in the ^1H NMR spectrum for their α -protons which is characteristic of this type of β -keto-*N*-acyl-oxazolidin-2-one.^[188] They also exhibited a new ^{13}C resonance at 211.2 ppm and 210.9 ppm which are characteristic of a ketone functionality. Their structure was further confirmed by the presence of three carbonyl signals in the IR spectrum (1782, 1716, 1697 cm^{-1}) and by high resolution mass spectroscopy (ES) which showed a molecular ion $[\text{M}+\text{H}]^+$ of 374.2329 (calculated 374.2326). Unfortunately it was not possible to separate these two diastereomers of ketone **286** by column chromatography.



Scheme 125. Mechanism of formation of diastereomeric ketones (4*R*)-**286a** and (4*S*)-**286b**

At low hydrogen pressure and low catalyst loading Brown's rhodium catalyst also resulted in formation of the ketone products **286**. However, increasing the hydrogen pressure to 4.5 bar reduced the formation of ketone products but still resulted in very little conversion to the desired product **284**. This supports the observation by Evans *et al.* that increasing the pressure of hydrogen suppresses the isomerisation pathway to the ketone product **286**. Higher catalyst loading of Brown's rhodium catalyst allowed complete conversion to the reduced products, however, crude ^1H NMR analysis showed the formation of four different products (signals at 3.42, 3.56, 3.68, 3.79 ppm corresponding to CHOH of each diastereomer). It was proposed that this 1: 1.1: 2.6: 1.1 mixture of diastereomers might

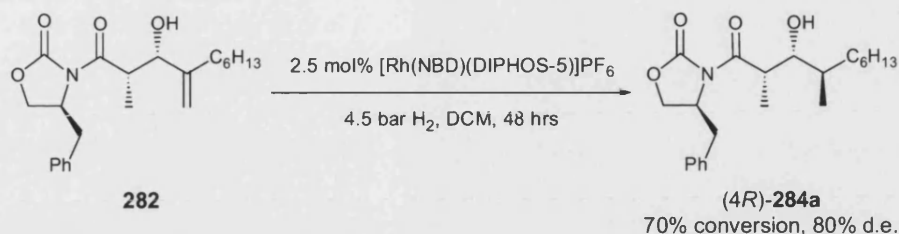
have been formed from isomerisation of aldol **282** to afford enol **287** that equilibrated to afford ketone **286**. Subsequent reduction would then afford the mixture of four diastereomers observed in the crude reaction mixture as shown in Scheme 126.



Scheme 126. Mechanism for formation of four possible diastereomers from hydrogenation of aldol **282**

In previously published reports Evans had noticed that at lower pressures the hydrogenation reaction of these type of aldols could be very slow, particularly with lower catalyst loadings.^[174] Because of this precedent, hydrogenation was carried out over 48 hours, at 4.5 bar hydrogen pressure using both catalysts at 2.5 mol% and 17.5 mol%. Reactions with Crabtree's iridium catalyst did not show any difference in product ratios to the results obtained after 24 hours. However, in the reaction with Brown's rhodium catalyst at 2.5 mol% loading, ^1H NMR spectroscopic analysis of the crude reaction mixture showed 70% conversion to reduced products at 80% diastereomeric excess (see Scheme 127). The major diastereomer was assigned as (4*R*)-**284a** as shown in Scheme 127, in concordance with Evans' previous results on related aldol substrates, and from consideration of the allylic strain arguments (see Scheme 104). Further investigations to

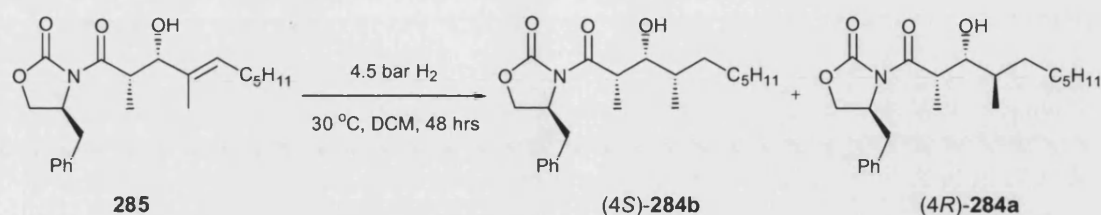
confirm the configurational assignment of the major aldol diastereomer produced in these reactions are discussed later in this thesis.



Scheme 127. Hydrogenation of *syn*-aldol **282** with 2.5 mol% rhodium catalyst over 48 hours

The 80% *d.e.* obtained for the formation of (4*R*)-**284a** was a promising result as it gave diastereoselectivities of a similar magnitude to the best previously achieved by Evans using comparable substrates at 4.5 bar. However, Evans' previous report required the use of very high pressures of hydrogen (44 bar) to achieve their results (82 – 88% *d.e.*), whilst they describe that the use of the same catalyst at atmospheric pressure resulted in much poorer diastereoselectivities (4 – 76% *d.e.*).^[170] It is important to note that the diastereomers formed in these hydrogenation reactions were easily separable by column chromatography, allowing access to diastereomerically pure products.

The isomerised aldol product **285** was also subjected to some exploratory reactions using the two hydrogenation catalysts (see Table 2.3). As indicated by Evans' previous studies and from conformational analysis arguments, (see Scheme 105) it was predicted that this starting material would favour the formation of the opposite diastereomer 4(*S*)-**284b** to that produced for hydrogenation of methylene aldol **282**.



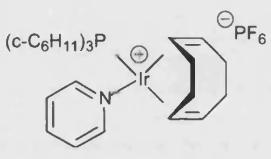
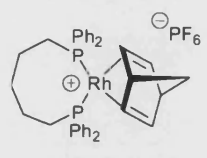
Catalyst	Loading (mol%)	Results
 Crabtree's	2.5	90% SM 285
	17.5	50:50 ketone 286 : product (4S)-284b 37% <i>d.e.</i>
 Brown's	2.5	50:50 SM 285 : product (4S)-284b 40% <i>d.e.</i>
	17.5	100% product (4S)-284b 64% <i>d.e.</i>

Table 2.3 Hydrogenation reactions using isomerised syn-aldol **285**

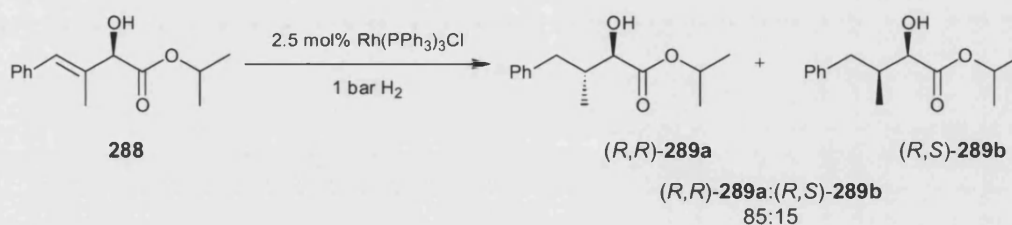
The results with Crabtree's iridium catalyst were once again disappointing, with little conversion to the desired reduced aldol product **284**, and a significant amount of the unwanted ketone products **286** being produced. With Brown's rhodium catalyst the results were improved, with low catalyst loading affording a mixture of starting material and hydrogenated aldol product **284** in 40% diastereomeric excess, whilst increasing the catalyst loading gave 100% conversion to cleanly afford the reduced products **284** in a reasonable 64% diastereomeric excess. This suggested that aldol **285**, in which the alkene was tri-substituted, was more stable than the methylene aldol **282** and therefore does not readily isomerise to give the ketone product, with consequent scrambling of stereocontrol.

These results showed that our unsaturated aldols **282** and **285** could undergo directed hydrogenation reactions in a similar manner to those described by Evans. Although

reactions with Crabtree's catalyst were disappointing in our hands, we had achieved comparable results to those reported by Evans using Browns catalyst $[\text{Rh}(\text{NBD})(\text{DIPHOS-5})]\text{PF}_6$, under significantly milder conditions.

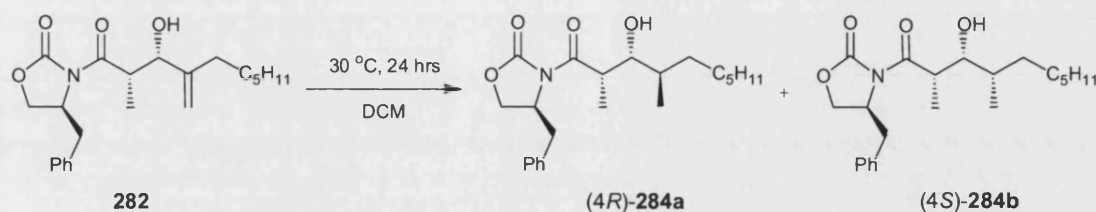
2.6.3 Hydrogenation reactions with Wilkinson's catalyst

In 1991 Simon *et al.* reported the use of Wilkinson's rhodium catalyst $\text{Rh}(\text{PPh}_3)_3\text{Cl}$ for the hydrogenation of allylic alcohol **288** to give chiral alcohols (*R,R*)-**289a** and (*R,S*)-**289b** in 70% diastereomeric excess (see Scheme 128).^[192]



Scheme 128. Use of Wilkinson's catalyst for the diastereoselective hydrogenation of allylic alcohol **288**

Consequently, it was decided to investigate whether Wilkinson's catalyst could also be used for the diastereoselective hydrogenation of our unsaturated aldol products **282** and **285**. Therefore aldol **282** was subjected to hydrogenation reaction under the same conditions previously used with Crabtree's and Brown's catalysts. The results of these hydrogenation reactions are summarised in Table 2.4.



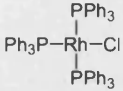
Catalyst	Loading (mol%)	Pressure	
		1 bar	4.5 bar
 Wilkinson's	2.5	50:50 SM 282 : product (4R)-284a	5:95 SM 282 : product (4R)-284a 60% <i>d.e.</i>
	17.5	100% product (4R)-284a 50% <i>d.e.</i>	100% product (4R)-284a 60% <i>d.e.</i>

Table 2.4 Hydrogenation screen using Wilkinson's catalyst

At low catalyst loading the hydrogenation reaction gave a mixture of starting material and reduced product with no evidence of any ketone products **286** having been produced. This suggested that the isomerisation pathway observed with Crabtree's and Brown's was not occurring with this catalyst. At 5 bar pressure there was 95% conversion to the reduced product which showed 60% diastereomeric excess by analysis of the crude ^1H NMR spectrum. Higher catalyst loading allowed for complete conversion to the desired products with 60% diastereomeric excess at 4.5 bar hydrogen pressure. These results showed an improvement on our initial results using this aldol substrate with Crabtree's and Brown's catalysts. These reactions were also repeated over a period of 48 hours, but showed no difference in the observed results, thus indicating that the hydrogenation reaction with Wilkinson's catalyst was occurring over a much faster timescale.

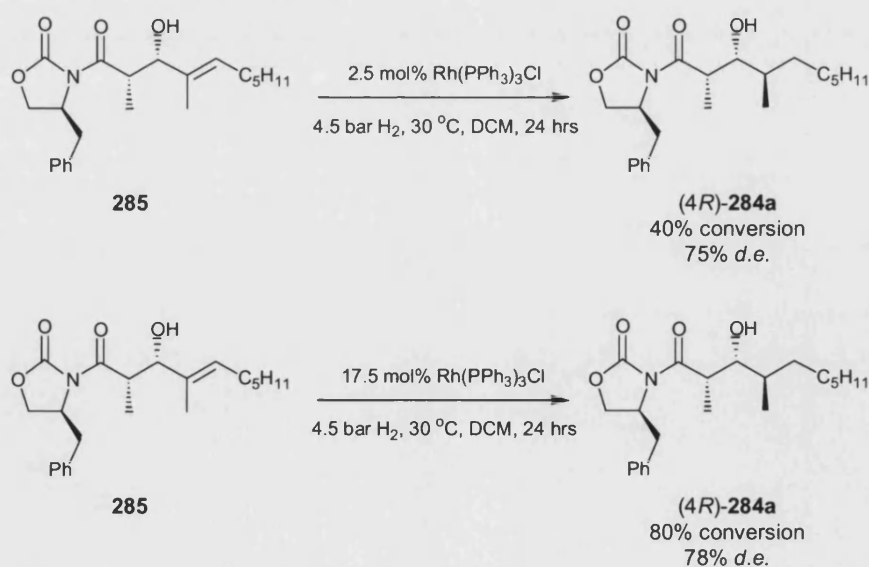
With these promising results in hand a screen of some common solvents was carried out using 17.5 mol% Wilkinson's catalyst at 4.5 bar hydrogen pressure for 24 hours. All reactions proceeded to 100% conversion, with the diastereomeric excesses of each reaction being calculated by integration of resolved peaks for each diastereomer in the ^1H NMR spectra (**(4R)-284a** CHOH at 3.56 ppm, **(4S)-284b** CHOH at 3.68 ppm) (see Table 2.5).

Solvent	Diastereomeric excess (%)
toluene	64
dichloromethane	60
ethyl acetate	50
tetrahydrofuran	44
ethanol	34
methanol	31

Table 2.5 Effect of solvents on hydrogenation of *syn*-aldol **282** using Wilkinson's catalyst

These results show that the choice of solvent had a significant effect on the diastereoselectivity of the hydrogenation reaction using Wilkinson's rhodium catalyst. The original solvent, dichloromethane showed one of the highest diastereoselectivities, with only toluene being higher (64%), whilst more polar solvents resulted in a dramatic reduction in the diastereoselectivity of this reaction.

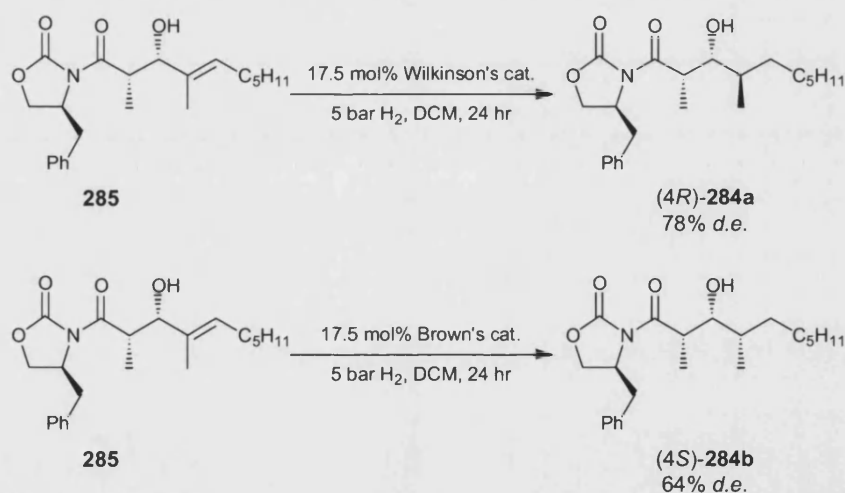
Hydrogenation reactions of alternative aldol **285** then attempted with Wilkinson's catalyst at 4.5 bar hydrogen pressure and at both catalyst loadings (see Scheme 129).



Scheme 129. Hydrogenation of isomerised aldol **285** using Wilkinson's catalyst

Interestingly with Wilkinson's rhodium catalyst, the conversion of aldol **285** to its reduced products was more sluggish, resulting in some recovery of starting material, however there was no evidence of any isomerised products indicating that aldol **285** was stable under these hydrogenation conditions. However, whilst the observed diastereoselectivity was high it was found to also result in formation of the same (4*R*)-**284a** diastereomer as produced previously for hydrogenation of methylene aldol **282**. This result was unexpected since allylic strain models would predict that the (4*S*)-**284b** diastereomer should have been favoured as had been observed previously for hydrogenation of aldol **285** with Brown's catalyst. In order to explain this observation it was proposed that sterics rather than a hydroxyl-directing effects might be important in controlling the facial selectivity of hydrogenation reactions with Wilkinson's catalyst, and further investigations into this hypothesis are discussed later in this thesis.

To conclude, the hydrogenation reactions of alternative aldol **285** were highly promising since they allowed the possibility of a divergent strategy where both aldol diastereomers (4*R*)-**284a** and (4*S*)-**284b** could be accessed using readily available aldol substrates and different catalysts under the same conditions (see Scheme 130).



Scheme 130. Catalyst controlled divergent strategy for the synthesis of both diastereomers of **284**

2.6.4 Assignment of stereochemistry

The stereochemistry of the major diastereomer arising from hydrogenation of methylene aldol **282** was assigned as the (4*R*)-product **284a** by comparison with Evans' precedent and from allylic strain models (see Scheme 104). Comparison of the ^1H NMR spectra of the two diastereomers of product **284** also supported this assignment with (4*R*)-**284a** exhibiting a larger coupling constant of $J_{(3,4)} = 8.7$ Hz characteristic of an *anti*-configuration of protons, compared to a smaller coupling constant ($J_{(3,4)} = 3.8$ Hz) for the *syn*-configuration of protons of (4*S*)-**284b** (see Figure 4). However, assigning stereochemistry from coupling constants in acyclic systems can be misleading, and therefore it was decided to confirm this configurational assignment by a correlation method.

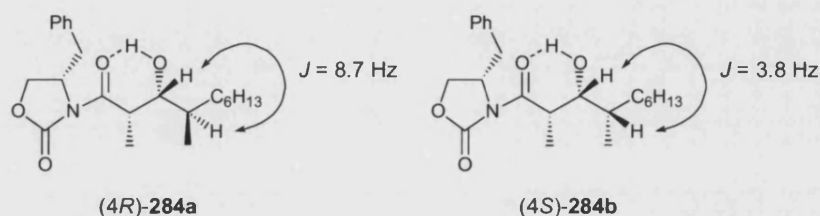
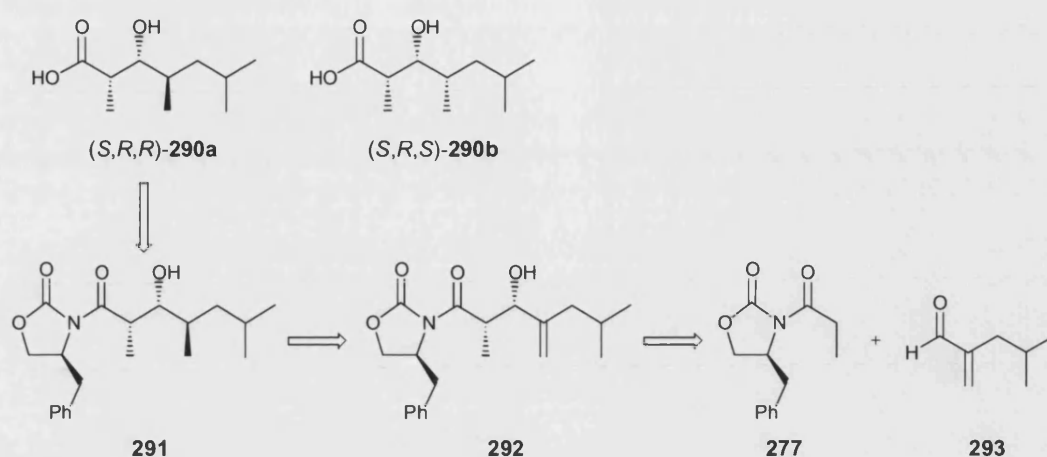


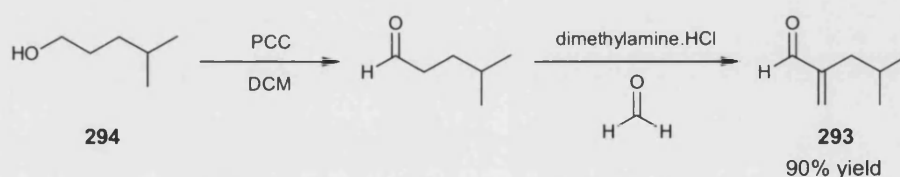
Figure 4. Comparison of $J_{(3,4)}$ coupling constants of 4(*R*)-**284a** and 4(*S*)-**284b**

Lipton *et al.* had recently reported the synthesis and characterisation of two diastereomers of 3-hydroxy-2,4,6-trimethylheptanoic acid (2*S*,3*R*,4*R*)-**290a** and (2*S*,3*R*,4*S*)-**290b**.^[193] Synthesis of one of these acids could potentially be achieved from aldol **291** that could be obtained using our hydrogenation reaction methodology, according to the retrosynthesis shown in Scheme 131. This would then enable us to unequivocally assign the stereochemistry of the major diastereomer of the hydrogenation reaction of aldol **291** arising from the hydrogenation reaction using Wilkinson's catalyst.



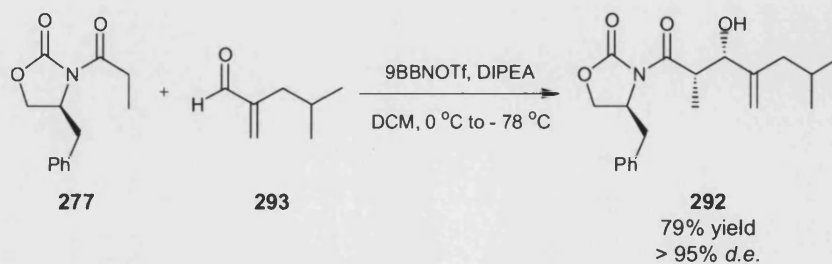
Scheme 131. Proposed retrosynthetic analysis for the synthesis of acid **290a**

Therefore, the required unsaturated methylene aldehyde **293** was synthesised in good yield by PCC oxidation of commercially available alcohol **294**, followed by a dehydrative Mannich type reaction with dimethylamine hydrochloride and formaldehyde as described previously (see Scheme 132).



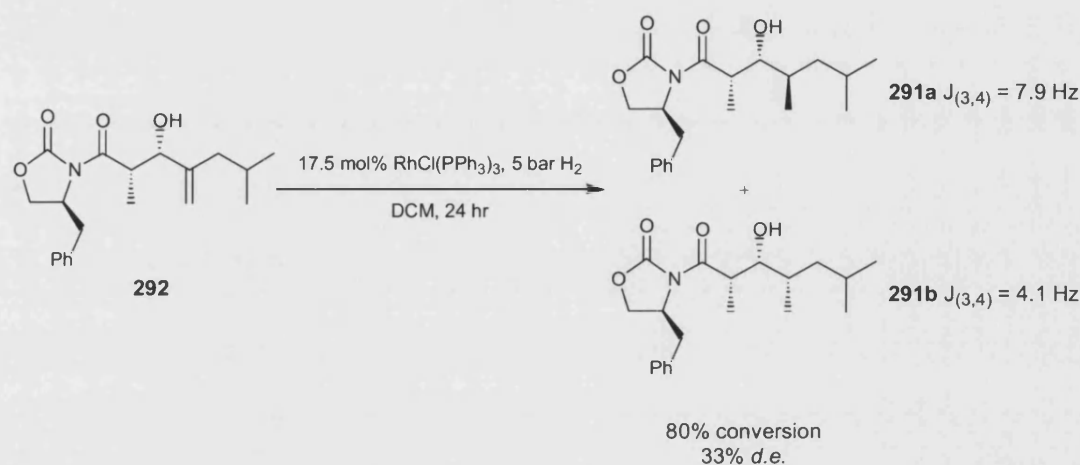
Scheme 132. Synthesis of α -methylene aldehyde **293**

This aldehyde **293** was then reacted with *N*-propionyl oxazolidinone **277** according to our established aldol procedure to yield the *syn*-aldol product **292** in good 79% yield and greater than 95% diastereoselectivity (see Scheme 133).



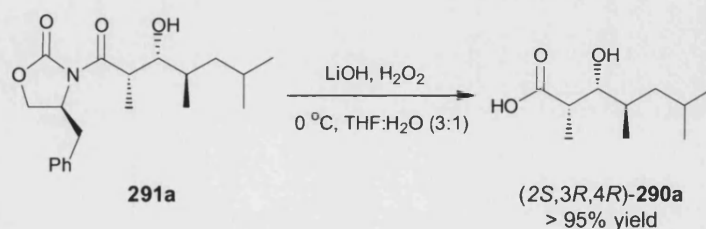
Scheme 133. Synthesis of *syn*-aldol **292**

This γ -unsaturated aldol **292** was then subjected to a hydrogenation reaction using 17.5 mol% Wilkinson's catalyst at 5 bar hydrogen pressure (see Scheme 134). After 24 hours the ^1H NMR spectrum of the crude product showed an approximately 80% conversion of aldol **292** to hydrogenated product **291**, in a disappointing 33% diastereomeric excess. However, examination of the ^1H NMR spectrum showed the major diastereomer produced in this reaction was structurally related to the major diastereomer produced previously for hydrogenation of aldol **282**.



Scheme 134. Hydrogenation of unsaturated aldol **292** using Wilkinson's catalyst

Attempts to separate these diastereomers via column chromatography proved difficult as both diastereomers and the starting aldol **292**, eluted very close together. However, painstaking chromatography enabled a small amount of the major diastereomer **291a** to be isolated which was then treated with lithium hydroperoxide to yield the desired acid **290a** as a single product in almost quantitative yield, without racemisation of any stereocentres (see Scheme 135).^[194]



Scheme 135. Hydrolysis of aldol **291a** with LiOOH to afford acid **290a**

By comparison with the spectroscopic data reported by Lipton *et al.* it was confirmed that our acid was indeed (2*S*,3*R*,4*R*)-**290a** with the ¹H NMR spectrum showing a doublet of doublets resonance at δ 3.65 ppm corresponding to the C3 proton ($J = 7.9, 3.4$ Hz) identical to the data previously reported by Lipton *et al.*. The product also showed a doublet of quartets at δ 2.72 ppm corresponding to the C2 proton as reported by Lipton *et al.*, however our observed coupling was $J = 7.2, 3.4$ Hz, rather than the $J = 3.5, 3.5$ Hz reported in the literature. By contrast, the (2*S*,3*R*,4*S*)-diastereomer **290b** was reported to exhibit an apparent triplet for the C3 proton resonance ($J = 5.5$ Hz) at δ 3.68 ppm and a doublet of quartets for the C2 proton at δ 2.72 ppm with a much larger coupling constant ($J = 6.0, 6.0$ Hz). Also, Lipton *et al.* had reported the optical rotation of the (2*S*,3*R*,4*R*)-isomer **290a** as $+ 24.4^\circ$ (c 1.0, CHCl₃) and the (2*S*,3*R*,4*S*)-isomer **290b** as $- 27.5^\circ$ (c 1.0, CHCl₃). The optical rotation of our isolated acid was measured as $+ 8.6^\circ$ (c 0.5, CHCl₃), which whilst being smaller in magnitude matched the sign of the specific rotation reported previously, supporting its assignment as the (2*S*,3*R*,4*R*)-diastereomer **290a**.

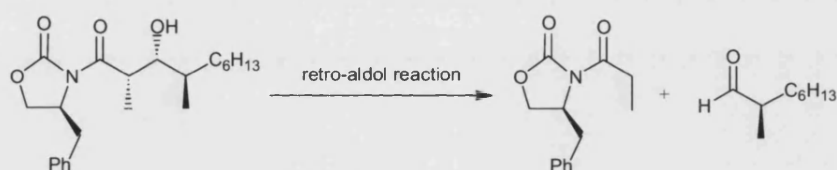
This correlation therefore provided good evidence that the major diastereomer produced in the hydrogenation of unsaturated aldol **282** using Wilkinson's catalyst was in fact the 4(*R*)-isomer, and as such it follows that the major diastereomer produced in the hydrogenation of isomerised aldol **285** using Brown's rhodium catalyst can be assigned as the opposite 4(*S*)-isomer.

2.7 Conclusions

This chapter has demonstrated my success in developing conditions for the synthesis of *syn*-aldols in good yield and with excellent diastereoselectivity, with good diastereoselectivities being obtained for their hydrogenation using Wilkinson's and Brown's catalysts. In order for our novel aldol/ directed hydrogenation/ retro-aldol strategy to be realised it was now necessary to develop conditions to successfully carry out retro-aldol reactions on our hydrogenated substrates.

Chapter 3: The retro-aldol reaction, elimination reactions and application to natural product synthesis

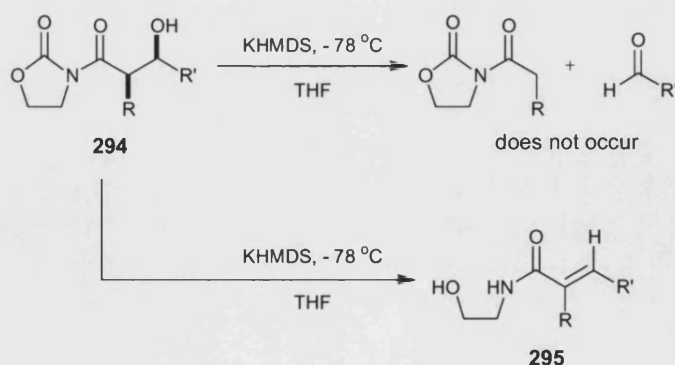
With promising results in hand for both the *syn*-aldol reaction and the directed hydrogenation reaction it was necessary to develop conditions that would enable our aldol substrates to undergo efficient retro-aldol cleavage to afford the desired chiral α -methyl aldehydes (see Scheme 136).



Scheme 136. Desired retro-aldol reaction

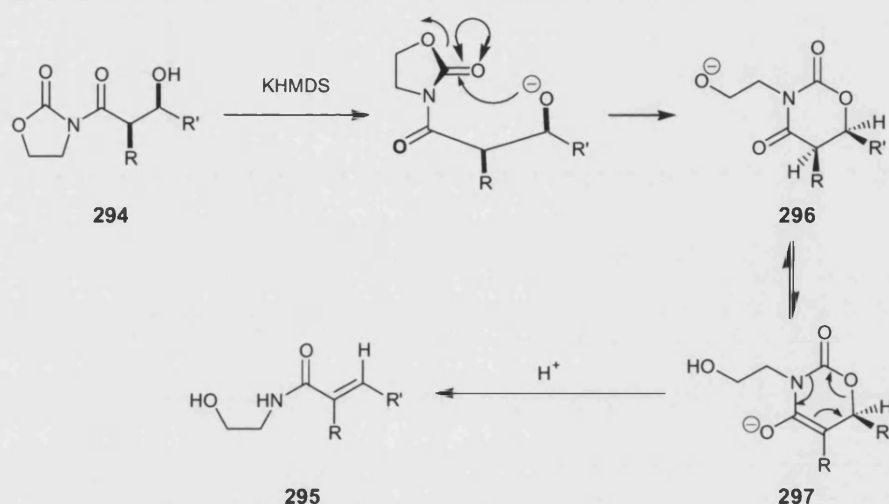
3.1 A novel β -elimination reaction

Previous work within our group had shown that racemic *syn*-aldol products such as **294** did not undergo anionic retro-aldol reactions when treated with a base such as KHMDS, instead undergoing a novel elimination reaction to yield α,β -unsaturated amide **295** as shown in Scheme 137.^[190,195]



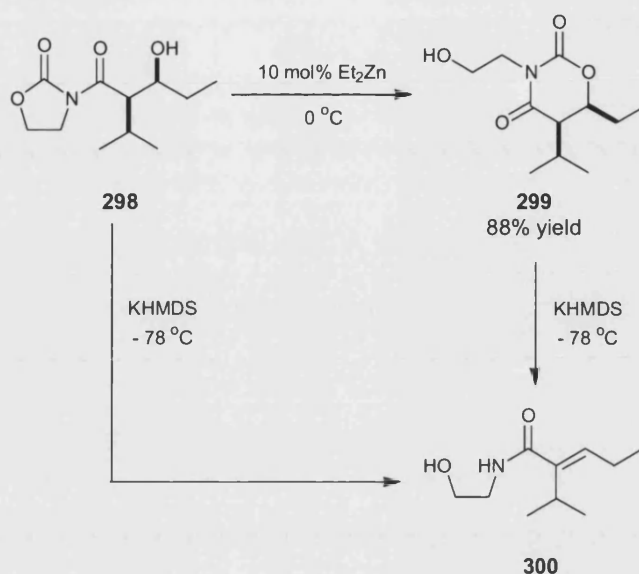
Scheme 137. Formation of novel α,β -unsaturated amide **295**

These α,β -unsaturated amides **295** were shown to arise via the cyclisation-elimination mechanism shown in Scheme 138. The hydroxyl group of aldol **294** undergoes deprotonation on addition of KHMDS to afford an alkoxide that attacks the endocyclic carbonyl to give an unstable cyclic oxazinane-*N*-dione **296**. Subsequent anion equilibration of **296** affords enolate **297** which then undergoes E1cB elimination of carbon dioxide to yield the observed (*E*)- α,β -unsaturated amide **295**.



Scheme 138. Mechanism of base induced cyclisation-elimination reaction

When 10 mol% of diethyl zinc was employed as a base to deprotonate aldol **298** it was found that the corresponding oxazinane-*N*-dione **299** intermediate could be isolated in good yield. When this oxazinane-2,4-dione was further treated with KHMDS it underwent elimination to yield the (*E*)-unsaturated amide **300** in greater than 90% diastereomeric excess (see Scheme 139). This result was in accordance with the mechanism proposed in Scheme 138, with the enolate of 1,3-oxazinane-2,4-dione **299** playing a key role in controlling the diastereoselectivity of the elimination reaction of *syn*-aldol **298**.

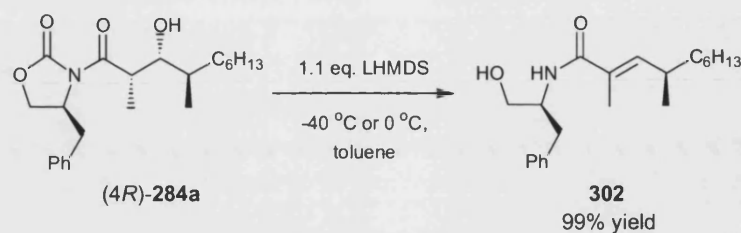


Scheme 139. Cyclisation and elimination reactions of *syn*-aldol **298**

3.2 Attempted retro-aldol reaction on chiral *syn*-aldol **284**

Bearing in mind the precedent that alkoxides of related *syn*-aldol substrates had undergone elimination reactions, it was proposed that introducing a benzyl substituent into the 4-position of the oxazolidinone ring might shield the *endo* cyclic carbonyl of *syn*-aldol **284** from intramolecular attack of its β -hydroxyl anion, thus allowing the desired retro-aldol pathway to proceed. Concurrent work carried out within the group on the retro-aldol reaction of cyclopropane aldols found that LHMDS was a superior base at preventing the formation of unwanted elimination products.^[166] Therefore, *syn*-aldol (4*R*)-**284a** was treated with 1.1 equivalents of LHMDS in toluene at a range of temperatures in an attempt to establish conditions where the retro-aldol reaction would occur preferentially.

At $-78\text{ }^\circ\text{C}$ no reaction occurred, enabling quantitative recovery of starting aldol (*R*)-**284a**. However at $-40\text{ }^\circ\text{C}$ and $0\text{ }^\circ\text{C}$, the lithium alkoxide of **284a** did not undergo the desired retro-aldol reaction but instead underwent the unwanted elimination reaction to afford α,β -unsaturated amide **302** in quantitative yield as a single (*E*)-diastereomer (see Scheme 140).



Scheme 140. Formation of (*E*)-unsaturated amide **302**

The structure of **302** was assigned as the (*E*)-isomer from our previous literature precedent and by analysis of its NOESY ^1H NMR spectra, which showed correlation between the two methyl groups, with no cross-peaks between the alkene proton and the methyl group as would be expected for its (*Z*)-isomer (see Figure 5).

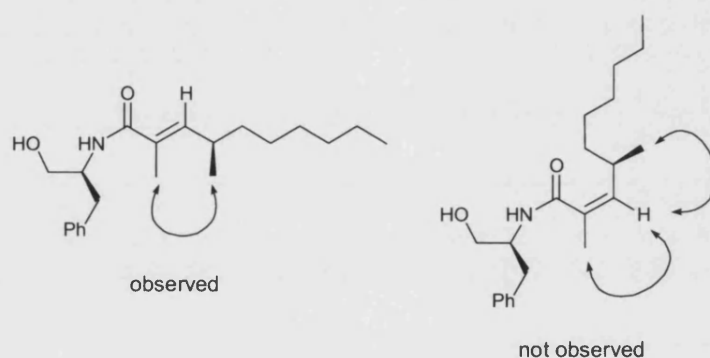
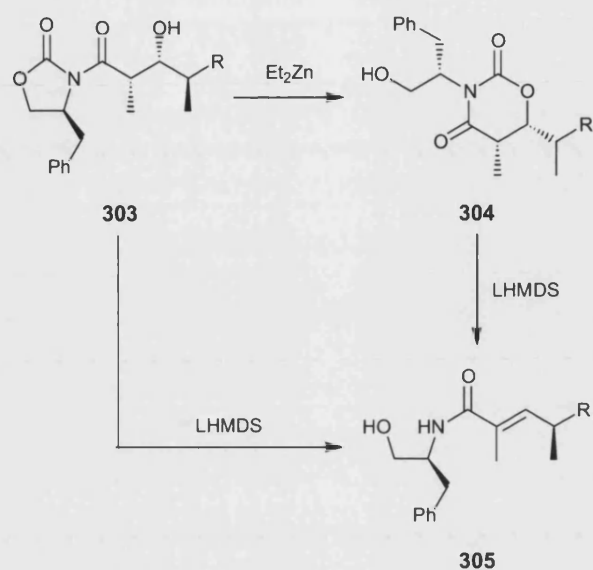


Figure 5. Observed NOESY ^1H NMR correlation of the (*E*)-isomer **302** and expected correlation for (*Z*)-isomer that was not observed

Since this was the first example of a chiral aldol product such as **303** undergoing elimination in a similar way to that observed previously for achiral β -hydroxy-*N*-acyloxazolidin-2-ones it was decided to investigate the scope and limitation of this cyclisation-elimination pathway for the synthesis of a range of chiral oxazinane-2,4-diones **304** and chiral α,β -unsaturated amides **305** (see Scheme 141).

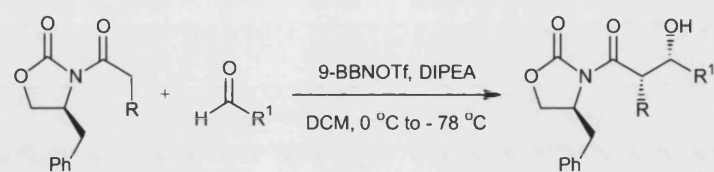


Scheme 141. Proposed synthesis of chiral oxazinane-2,4-diones and chiral α,β -unsaturated amides from chiral aldol products such as **303**

3.3 Synthesis of chiral *N*-2-hydroxyethyl-1,3-oxazinane-2,4-diones

Benzo-1,3-oxazinane-2,4-diones have often been screened for activity as potential drug targets,^[196-200] and as a result there are a range of synthetic methods available for their preparation.^[201-204] However, synthetic routes towards chiral 1,3-oxazinane-2,4-diones were much less well explored and therefore our investigations into their synthesis would provide a valuable contribution to this area.

Therefore, a range of *N*-acyloxazolidin-2-one *syn*-aldols were prepared in good isolated yield in greater than 90% *d.e.* using our previously established boron enolate *syn*-aldol procedure (see Table 3.1).



<i>syn</i> -aldol	R	R ¹	Yield (%)
306	Me	Cyclohexyl	90
280	Me	Et	91
307	ⁱ Pr	Et	72
308	Me	C(Et)=CH ₂	83
309	Me	Ph	75
282	Me	C(C ₆ H ₁₃)=CH ₂	85
310	Me	<i>p</i> -MeOC ₆ H ₄	68
311	Ph	C(C ₆ H ₁₃)=CH ₂	70

Table 3.1 Synthesis of *syn*-aldol products

These *syn*-aldols were then treated with diethyl zinc in dichloromethane at room temperature to afford their corresponding chiral oxazinane-2,4-diones **312** – **319** as described in Table 3.2 and Table 3.3. It was found that simple aliphatic *syn*-aldols **306**, **280** and **307** underwent rearrangement cleanly using 10 mol% diethyl zinc over a period of two hours, to yield *syn*-1,3-oxazinane-2,4-diones **312** – **314** that could be isolated in high yield and with excellent diastereoselectivity (see Table 3.2).



1,3-oxazinane-2,4-dione	R	R ¹	Conditions	Yield (%)	<i>d.e.</i> (%)
312	Me	Cyclohexyl	10 mol%, 2 hr	94	> 95
313	Me	Et	10 mol%, 2 hr	94	> 95
314	ⁱ Pr	Et	10 mol%, 2 hr	90	> 95

Table 3.2 Synthesis of chiral 1,3-oxazinane-2,4-diones

The structure and configuration of oxazinane-2,4-diones **312** – **314** was confirmed by HMBC ^1H - ^{13}C correlation spectra which showed cross-peaks between the ^{13}C resonance of the C2 carbonyl and the ^1H resonances of H6 and *N*-CH protons (for an example see Figure 6). Their structures were also supported by the small ^1H NMR *J* coupling between the H5 and H6 protons (3.0 – 4.5 Hz), and a large upfield shift in the H5 proton resonance in comparison to the corresponding resonance of the parent *syn*-aldol product.

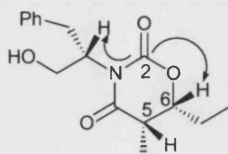


Figure 6. Selected resonances from HMBC ^1H - ^{13}C correlation experiment

Rearrangement reactions involving treatment of chiral aldol products containing β -aryl- or β -alkene substituents using catalytic amounts of diethyl zinc proved much less successful (see Table 3.3).

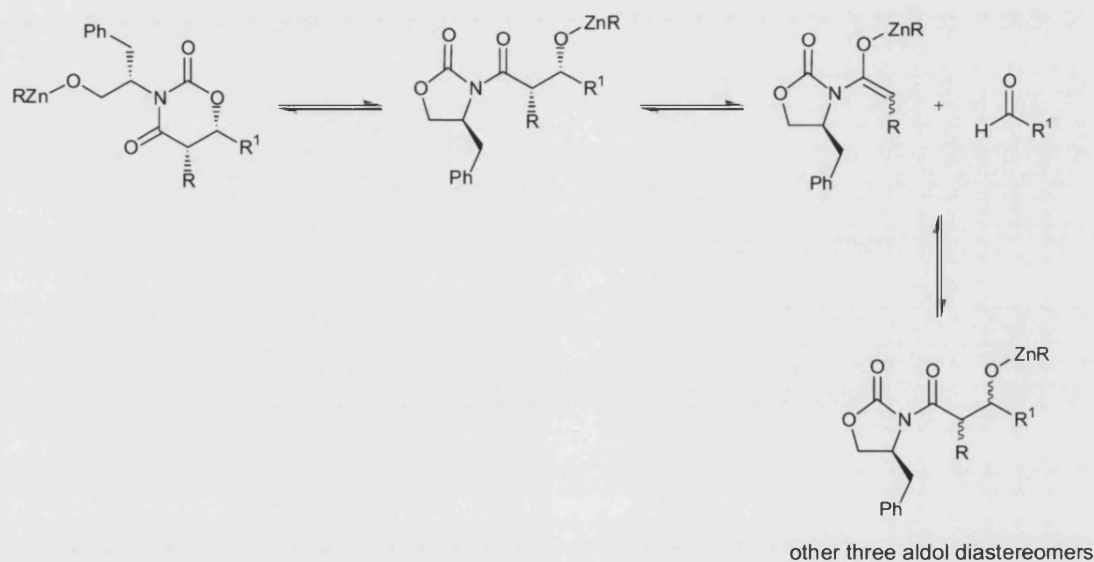


1,3-oxazinane-2,4-dione	R	R ¹	Conditions	Yield (%)	d.e. (%)
315	Me	C(Et)=CH ₂	10 mol%, 2 hr	17 ^a	> 85
315	Me	C(Et)=CH ₂	100 mol%, 2 hr	60	> 90
316	Me	Ph	10 mol%, 2 hr	35	> 90
317	Me	C(C ₆ H ₁₃)=CH ₂	10 mol%, 2 hr	20 ^a	–
317	Me	C(C ₆ H ₁₃)=CH ₂	10 mol%, 16 hr	20 ^a	–
317	Me	C(C ₆ H ₁₃)=CH ₂	100 mol%, 16 hr	20 ^a	–
318	Me	<i>p</i> -MeOC ₆ H ₄	10 mol%, 2 hr	15 ^a	–
318	Me	<i>p</i> -MeOC ₆ H ₄	100 mol%, 16 hr	15 ^a	–
319	Ph	C(C ₆ H ₁₃)=CH ₂	10 mol%, 2 hr	–	–

^a yield shown is NMR conversion

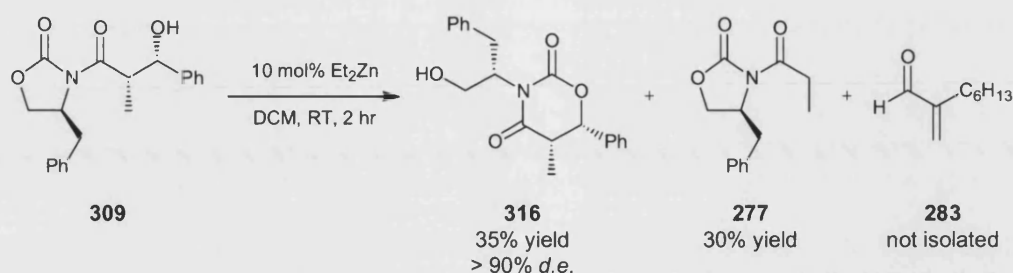
Table 3.3 Reaction of β -aryl and β -alkene aldols with diethyl zinc

In the case of aldol **308** employing a stoichiometric amount of diethyl zinc improved the overall yield of **315** from 17% to 60% yield. Unfortunately the same effect was not observed for aldols **282** or **310** where ^1H NMR analysis of the crude reaction product revealed the presence of a number of diastereomeric aldol products which made it difficult to analyse the outcome of the rearrangement reaction. This led us to conclude that the rearrangement reactions of these types of chiral aldol substrate were reversible, with an equilibrium distribution of aldol/ 1,3-oxazinane-2,4-diones occurring via reversible retro-aldol reaction (see Scheme 142), the extent of which depended on the nature of their α - and β -substituents.



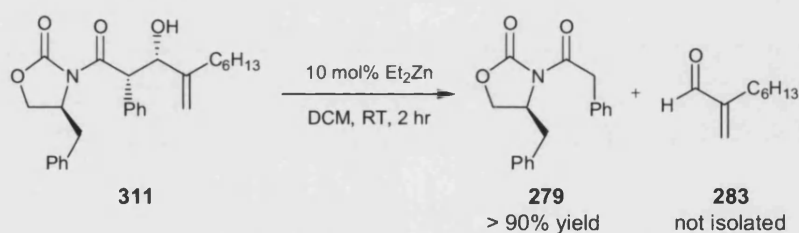
Scheme 142. Mechanism for the reversible rearrangement reaction leading to scrambling of the α - and β -stereocentres of the aldol product

This hypothesis was confirmed when aldol **309** was treated with 10 mol% diethyl zinc, which gave 1,3-oxazinane-2,4-dione **316** in high diastereomeric excess but in a low 35% yield due to a competing retro-aldol reaction occurring to afford *N*-propionyl oxazolidinone **277** (see Scheme 143).



Scheme 143. Competing retro-aldol of *syn*-aldol **309** with 10 mol% diethyl zinc

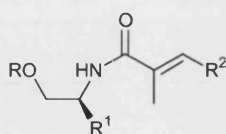
The presence of this competing retro-aldol reaction was also confirmed for *syn*-aldol **311** which underwent a clean retro-aldol reaction to yield *N*-phenylacetyl oxazolidinone **279** and aldehyde **283** when treated with diethyl zinc under standard conditions (see Scheme 144). Therefore it appears that the added electronic stabilisation of the α -aryl substituent of the zinc enolate of **279** allows the retro-aldol pathway to dominate in the reaction of this *syn*-aldol **311** with diethyl zinc.



Scheme 144. Retro-aldol reaction of *syn*-aldol **311** using 10 mol% diethyl zinc

3.4 Synthesis of Semiplenamide natural products

The novel base induced cyclisation-elimination methodology that had been established was then exploited to synthesise a range of α,β -unsaturated amidic natural products. In 2003 Gerwick *et al.* had reported the isolation of a series of novel semiplenamide metabolites from a Papua New Guinea collection of the marine cyanobacterium *Lyngbya semiplena*.^[205] The structures of these natural products are shown in Scheme 145, and were shown to exhibit a range of biological activity including affinity for the cannabinoid CB₁ receptor and inhibition of the anandamide membrane transporter in the rat model.



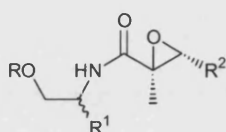
Semiplenamide A; R = H, R¹ = H, R² = (3*E*)-*n*-C₁₇H₃₃

Semiplenamide B; R = Ac, R¹ = H, R² = (3*E*)-*n*-C₁₇H₃₃

Semiplenamide C; R = H, R¹ = Me, R² = *n*-C₁₃H₂₇

Semiplenamide D; R = Ac, R¹ = Me, R² = *n*-C₁₇H₃₅

Semiplenamide E; R = Ac, R¹ = Me, R² = *n*-C₁₅H₃₁

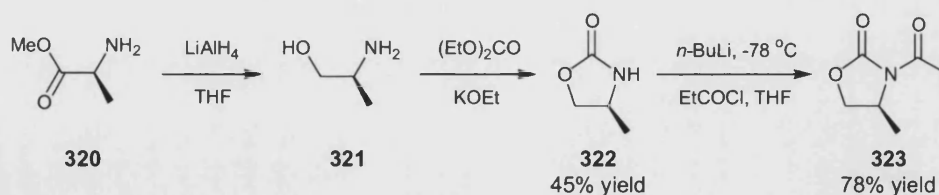


Semiplenamide F; R = H, R¹ = Me, R² = *n*-C₁₅H₃₁

Semiplenamide G; R = Ac, R¹ = Me, R² = *n*-C₁₅H₃₁

Scheme 145. Structures of Semiplenamides A-G

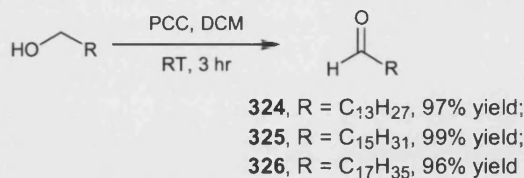
It was proposed that our novel cyclisation-elimination methodology was ideally suited for the synthesis of the core fatty acid amide fragments of a number of these semiplenamides. Therefore, L-alanine methyl ester **320** was reduced with lithium aluminium hydride in diethyl ether and the resulting (*S*)-amino alcohol **321** cyclised with diethyl carbonate to give (*S*)-4-methyl-oxazolidinone **322** in 45% overall yield. The oxazolidinone **322** was then deprotonated with butyl lithium at -78 °C before addition of propionyl chloride to yield *N*-propionyl oxazolidinone **323** in 78% yield (see Scheme 146).



Scheme 146. Synthesis of *N*-propionyl oxazolidinone **323**

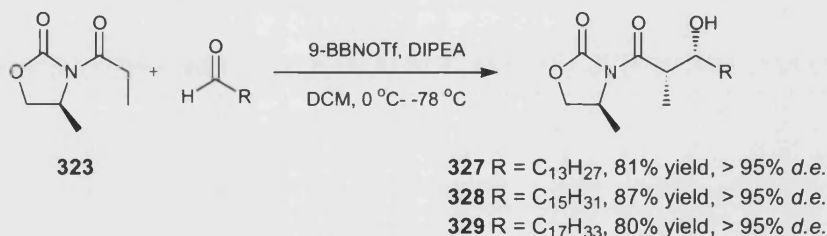
Before carrying out the aldol reaction the aldehydes **324** – **326** required for the natural product synthesis were synthesised from the corresponding commercially available

primary alcohols via oxidation with pyridinium chlorochromate in excellent 96 – 99% yields (see Scheme 147).



Scheme 147. Synthesis of required aldehydes **324** – **326**

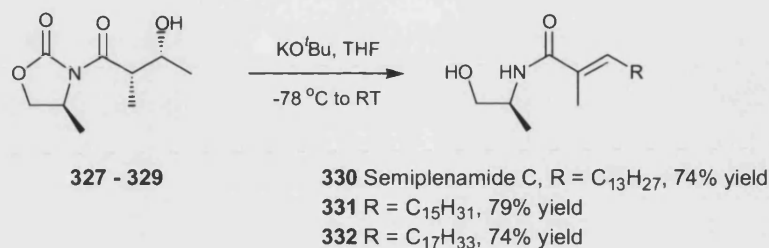
N-propionyl oxazolidinone **323** was then subjected to our *syn*-aldol conditions, involving addition of 1.1 equivalents of 9-BBNOTf and diisopropylethylamine in DCM at 0 °C, followed by cooling to -78 °C and addition of the appropriate aldehyde **324** – **326**. This produced the desired *syn*-aldol products **327** – **329** in good yields and high diastereoselectivity (see Scheme 148). The *syn*-stereochemistry was confirmed by the small ¹H NMR J coupling constants between the α- and β-protons of 2.0 – 3.0 Hz. The stereoselectivity in this aldol reaction was particularly noteworthy considering the configuration of the *syn*-aldol was controlled by the relatively sterically undemanding (4*S*)-methyl substituent on the oxazolidinone ring.



Scheme 148. Synthesis of *syn*-aldol products **327** – **329**

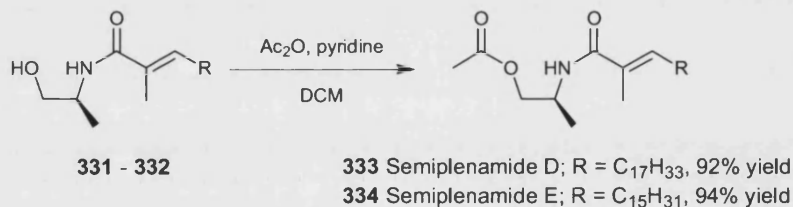
Treatment of these *syn*-aldol products **327** – **329** with KHMDS or LHMDS initially resulted in poor yields of α,β-unsaturated amide products **330** – **332** which was thought to be due to a competing retro-aldol pathway occurring, as evidenced by the presence of significant amounts of the respective aldehyde and *N*-propionyl oxazolidin-2-one **323** in the ¹H NMR spectrum of the crude product. However, changing the base used for deprotonation of the *syn*-aldols to potassium *tert*-butoxide at -78 °C afforded a clean

β -elimination reaction to give semiplenamide C **330** and the related unsaturated products **331** and **332** as precursors to semiplenamides D and E, in good yield after column chromatography (see Scheme 149).



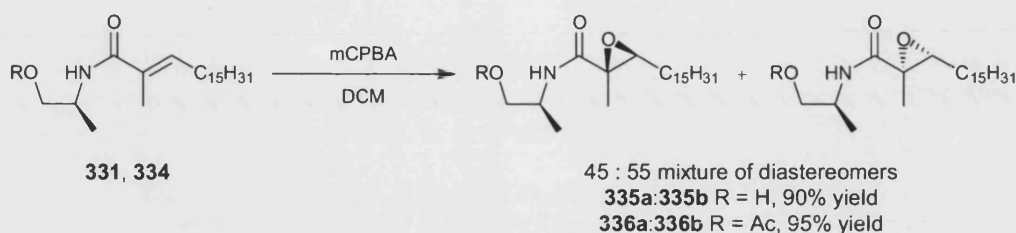
Scheme 149. Synthesis of α,β -unsaturated amides **330** – **332**

Treatment of α,β -unsaturated amides **331** and **332** with pyridine in acetic anhydride and dichloromethane, according to the general *O*-acylation procedure previously described by Vega-Pérez *et al.*,^[206] resulted in clean formation of semiplenamide D **333** and semiplenamide E **334** in excellent 92 – 94% yield, which were easily isolated by column chromatography (see Scheme 150).



Scheme 150. Synthesis of semiplenamides D **333** and E **334**

Treatment of α,β -unsaturated amides **331** and **334** with mCPBA in DCM allowed for non-stereoselective formation of a 45:55 mixture of the diastereomers of epoxy alcohols **335a:335b** and epoxy acetates **336a:336b** in excellent 90 – 95% yield (see Scheme 151). ¹H NMR spectra of these compounds revealed the presence of singlet resonances at δ 1.55 ppm corresponding to the methyl substituent of the epoxide ring and a triplet resonance at δ 2.83 ppm corresponding to the C-H of the epoxide ring. In addition ¹³C NMR spectra exhibit signals at δ 60.0 and 63.8 ppm characteristic of the epoxide functionality, with paired signals in the carbon spectrum indicating the presence of two diastereomers of product.



Scheme 151. Synthesis of diastereomeric mixtures containing semiplenamides F **335** and G **336**

Unfortunately repeated attempts to separate these epoxide diastereomers by chromatography proved unsuccessful. However, comparison of the ^1H NMR spectrum of the diastereomeric mixture of **335a:335b** and **336a:336b** with NMR data reported by Gerwick *et al.* for the corresponding natural products, clearly revealed that the minor diastereomers produced in our epoxidation reactions corresponded to the natural products and enabled us to confirm their configuration as shown in Figure 7.

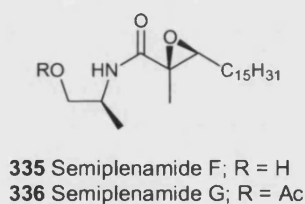


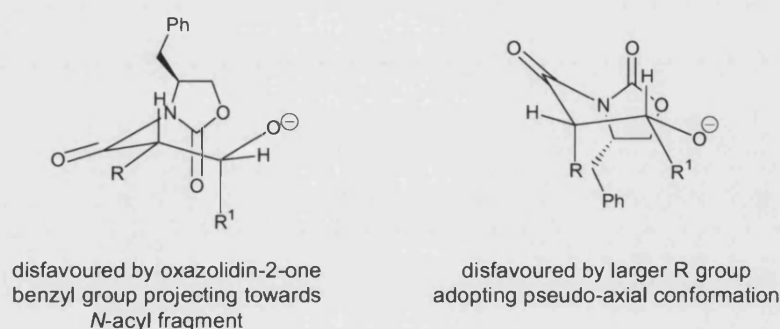
Figure 7. Confirmed structures of semiplenamides F and G

3.5 Further attempts at the retro-aldol reaction

Since I had shown that treatment of chiral *syn*-aldol **284** with base resulted in elimination in the same manner as achiral oxazolidin-2-one **294**, it was necessary to modify the structure of our chiral auxiliary so that the retro-aldol reaction pathway would predominate.

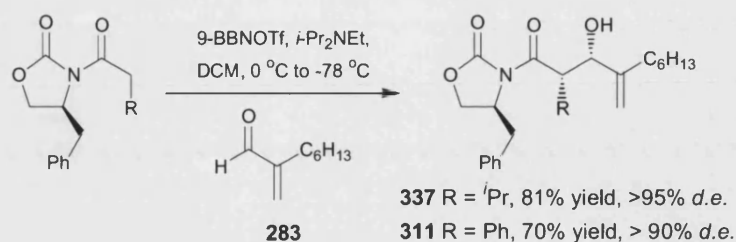
3.5.1 Probing the reactivity of α -phenyl and α -isopropyl aldols

It was proposed that a *syn*-aldol substrate containing a more sterically demanding substituent in its α -position might allow the retro-aldol reaction to be favoured over the cyclisation-elimination pathway. This was because it was thought that steric interactions between the α -substituent (R) and the benzyl substituent of the oxazolidin-2-one fragment would result in the aldol adopting chair-like conformations that would disfavour the elimination reaction from occurring, thus allowing the retro-aldol reaction to predominate (see Scheme 152).



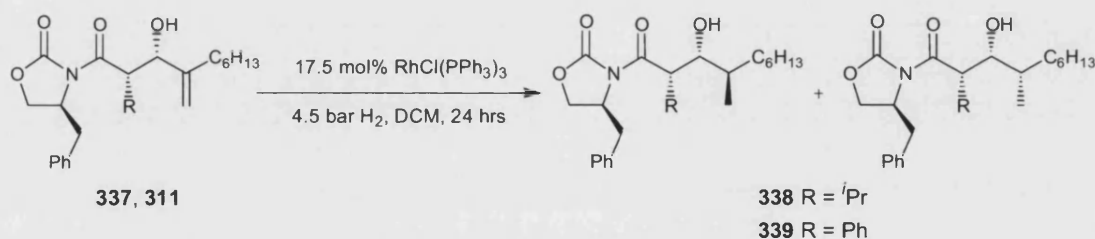
Scheme 152. Both conformers required for β -elimination disfavour elimination reaction

Syn-aldols **337** and **311** were therefore prepared using our established boron enolate procedure in order to test this hypothesis. Aldol **337** was synthesised in high yield and excellent diastereoselectivity (see Scheme 153), however whilst α -phenyl-substituted aldol **311** was formed in good conversion only small amounts of the desired aldol product could be isolated after column chromatography. This was thought to be due to the fact that the aldol **311** underwent a premature retro-aldol reaction on acidic silica. This was confirmed by adsorbing the *syn*-aldol **311** onto silica overnight which resulted in isolation of large amounts of *N*-phenylacetyl oxazolidinone **279** and oxazolidinone **276** on work-up. However, carrying out chromatography using neutral alumina as the stationary phase, resulted in isolation of a higher 70% yield of the desired aldol **311**.



Scheme 153. Synthesis of alternative unsaturated aldols

Both aldols **337** and **311** were subjected to hydrogenation reaction using Wilkinson's catalyst according to the standard procedure as shown in Scheme 154. Unfortunately, crude ^1H NMR spectroscopic analysis of these hydrogenation reactions proved to be difficult to interpret as the characteristic H3/H4 protons of the mixture of diastereomers (2*S*,3*R*,4*R*)-**338a** and (2*S*,3*R*,4*S*)-**338b** and (2*S*,3*R*,4*R*)-**339a** and (2*S*,3*R*,4*S*)-**339b** were not resolved in their ^1H NMR spectra, as they had been previously for corresponding diastereomers of the α -methyl substituted aldol **284**.



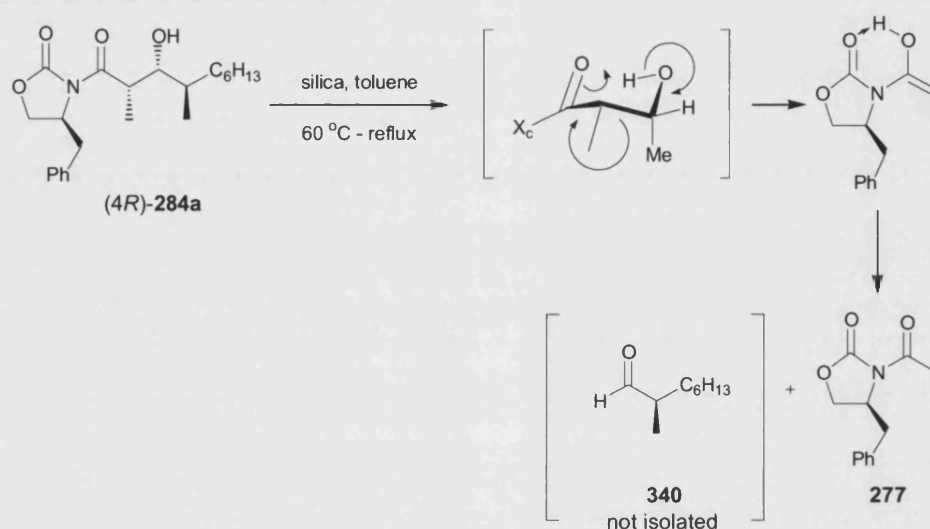
Scheme 154. Hydrogenation reactions using alternative α -substituted *syn*-aldols

Therefore, it was decided that aldols **337** and **311** would be difficult substrates for optimising the hydrogenation procedure, and as a consequence it was decided to explore an alternative approach to fixing the retro-aldol problem.

3.5.2 Investigation of a thermal retro-aldol procedure

Due to the ease with which α -phenyl aldol **311** had previously undergone retro-aldol reaction on exposure to silica, it was proposed that heating methyl-substituted *syn*-aldol **284** in the presence of silica might allow a thermal retro-aldol reaction to occur, thus eliminating the need to use basic conditions. Diastereomerically pure aldol (4*R*)-**284a** was

refluxed in toluene with silica for 5 hrs, with ^1H NMR spectroscopic analysis showing formation of *N*-propionyl oxazolidinone **277**, indicating that the retro-aldol reaction had occurred (see Scheme 155). However, all attempts to isolate the desired α -methyl aldehyde **340** from these thermal retro-aldol reactions at a range of temperatures were unsuccessful, with no resonance corresponding to an aldehyde proton being visible in the ^1H NMR spectra of the crude reaction products.



Scheme 155. Desired thermal retro-aldol reaction on silica

It was proposed that my inability to isolate volatile aldehyde **340** from these thermal retro-aldol reactions might be a consequence of its loss during reaction work-up. A thermal retro-aldol was therefore attempted by heating neat aldol *4(R)*-**284** to 205 $^\circ\text{C}$ in a Kugelrohr microdistillation apparatus with the distillation bulb cooled using an acetone/dry ice coolant. Once again although the ^1H NMR spectrum of the crude product showed a good yield of the *N*-propionyl oxazolidinone **277**, very little of the desired aldehyde **340** was present.

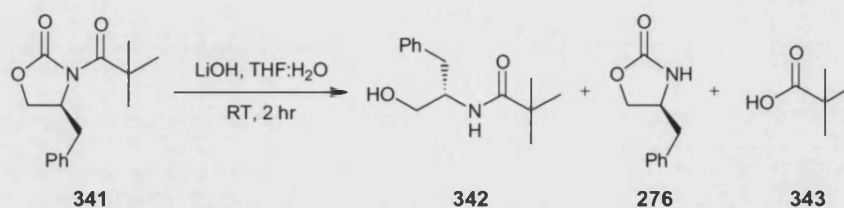
3.6 Successful retro-aldol reactions

Clearly, the ability to identify conditions that would enable successful retro-aldol reaction was the key to the success of our novel three step strategy for the synthesis of chiral

aldehydes. It was therefore necessary to suppress the competing cyclisation/elimination reaction and this was ultimately achieved using a strategy involving blocking intramolecular attack of the β -alkoxide at the ring carbonyl of the oxazolidin-2-one fragment.

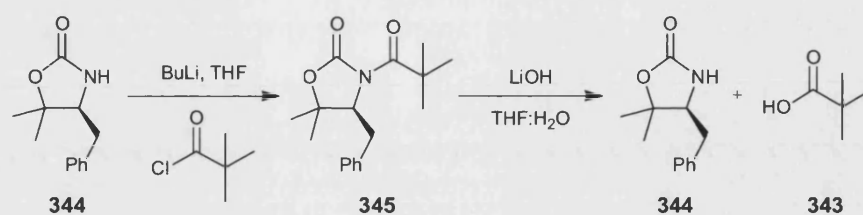
3.6.1 Use of the SuperQuat auxiliary

There was significant literature precedent describing the susceptibility of the endocyclic carbonyl of simple oxazolidin-2-ones to intermolecular nucleophilic attack. For example, Davies *et al.* had reported that sterically hindered *N*-pivaloyl oxazolidin-2-one **341** underwent competing endocyclic cleavage on treatment with lithium hydroxide to afford a mixture of a secondary amide **342** and the exocyclic cleavage products pivalic acid **343** and oxazolidin-2-one **276** (see Scheme 156).^[207]



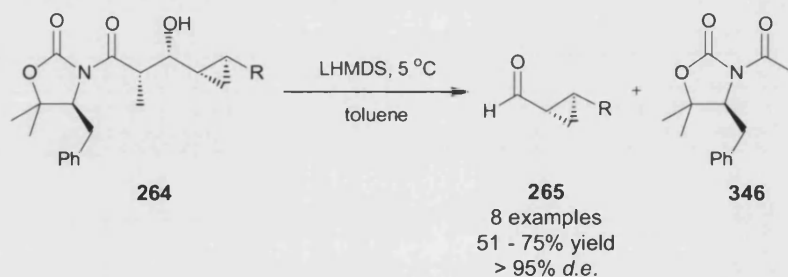
Scheme 156. Endocyclic cleavage of *N*-pivaloyl oxazolidin-2-one **341**

In this cleavage reaction the steric demands of the large tertiary butyl group were proposed to block attack of the incipient nucleophile at the exocyclic carbonyl, and therefore competing attack of the nucleophile at the endocyclic carbonyl of the oxazolidin-2-one fragment occurs. To overcome this problem, Davies *et al.* developed a new class of chiral oxazolidin-2-one known as the SuperQuat auxiliary **344** (see Scheme 157).^[208] This new oxazolidin-2-one contains a *gem*-5,5-dimethyl group which was designed to block the trajectory of attack of nucleophiles at the endocyclic carbonyl, resulting in clean exocyclic cleavage, even in the presence of the bulky tertiary butyl group (see Scheme 157).



Scheme 157. Exclusive exocyclic cleavage of *N*-pivaloyl SuperQuat **345**

The SuperQuat auxiliary had shown excellent levels of stereocontrol in the *syn*-aldol reaction and during the course of my studies another member of the SDB group demonstrated that alkoxides of *syn*-aldols derived from SuperQuat oxazolidin-2-ones underwent clean anionic retro-aldol reactions to afford chiral aldehydes. For example, treatment of SuperQuat derived cyclopropane-aldol **264** with LHMDS in toluene at 5 °C resulted in a clean retro-aldol reaction to yield cyclopropane carboxaldehyde **265** and *N*-propionyl oxazolidin-2-one **346** (see Scheme 158).^[166]



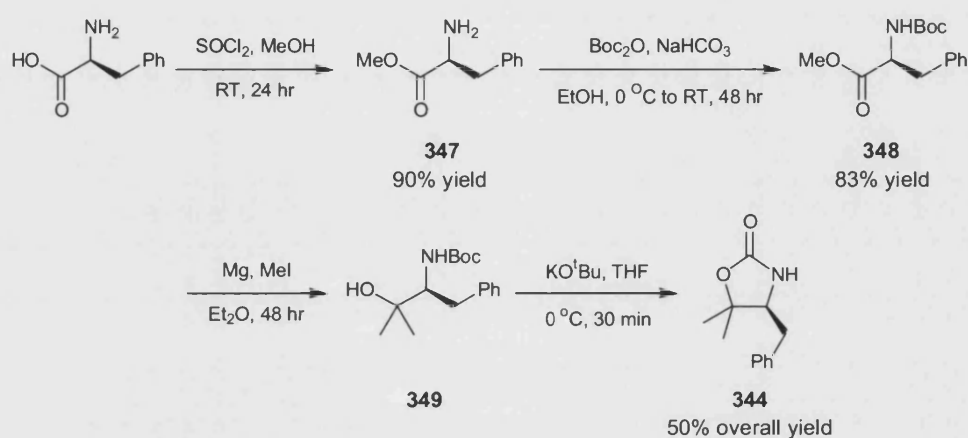
Scheme 158. Successful retro-aldol reaction of SuperQuat derived aldol **264**

Therefore, it was decided to employ the SuperQuat oxazolidin-2-one as a chiral auxiliary fragment for our aldol/ hydrogenation/ retro-aldol protocol since the presence of the *gem*-dimethyl fragment should serve to suppress any competing elimination reaction pathway during the retro-aldol reaction.

3.6.2 Synthesis of the SuperQuat auxiliary

The SuperQuat oxazolidin-2-one **344** was synthesised according to the procedure previously developed by Davies *et al.*^[208] (*S*)-phenylalanine was converted into its methyl ester by treatment with thionyl chloride in methanol to afford **347** in good 90% yield. The

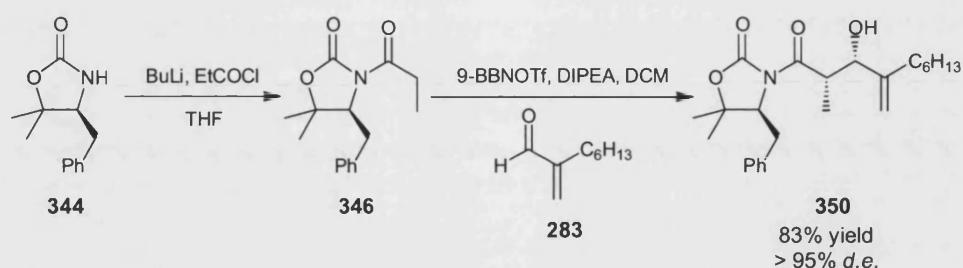
crude product was treated with Boc-anhydride and sodium hydrogen carbonate to give *N*-Boc-protected ester **348** in 83% yield without the need for further purification. Treatment of **348** with excess methyl magnesium iodide afforded alcohol **349**, although yields of this Grignard reaction were somewhat variable due to difficulties in isolating the *N*-Boc-amino alcohol during work up. Treatment of **349** with potassium *tert*-butoxide gave an alkoxide that cyclised intramolecularly onto the carbonyl of the *N*-Boc fragment to afford 5,5-dimethyl-(*S*)-4-benzyl oxazolidin-2-one **344** in a good 50% overall yield (see Scheme 159).



Scheme 159. Synthesis of SuperQuat auxiliary **344**

3.6.3 *Syn*-aldol reactions of SuperQuat auxiliaries

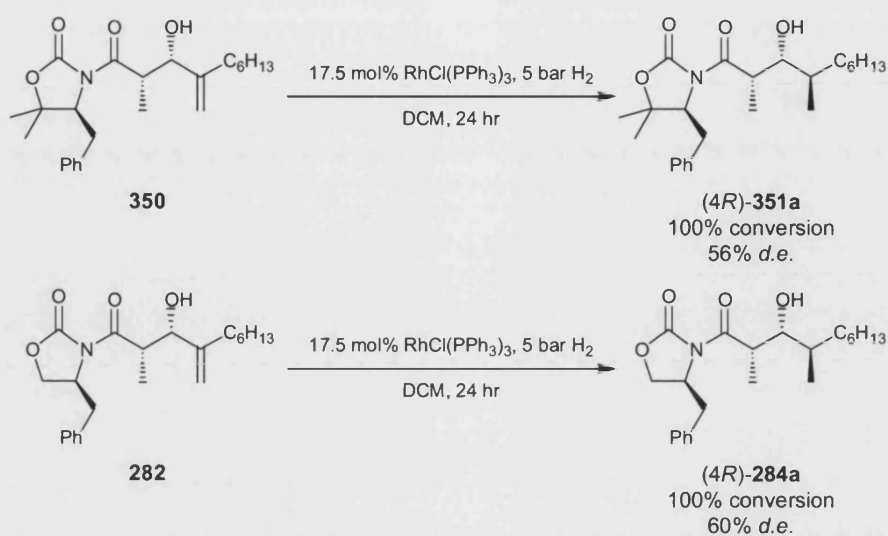
To confirm that the SuperQuat auxiliary **344** would perform similarly under our *syn*-aldol conditions oxazolidin-2-one **344** was acylated with propionyl chloride to afford *N*-propionyl oxazolidin-2-one **346**, which was then reacted with 9-BBNOTf, diisopropyl ethylamine and α,β -unsaturated aldehyde **283** in dichloromethane to produce *syn*-aldol product **350** in 83% yield and > 95% diastereomeric excess as determined by analysis of the ^1H NMR spectrum of the crude product (see Scheme 160). The resultant aldol product **350** was assigned as the *syn*-diastereomer by the small coupling constant $J_{(2,3)} = 3.4$ Hz between its α - and β -protons as described previously.



Scheme 160. Formation of *syn*-aldol product **350** derived from SuperQuat auxiliary **344**

3.6.4 Hydrogenation reaction with SuperQuat derived aldol product

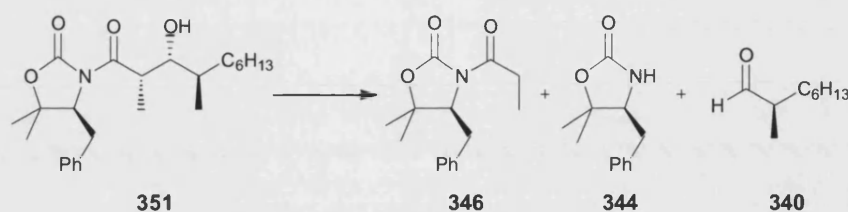
It was expected that the *gem*-dimethyl group of the SuperQuat auxiliary was unlikely to interfere with the diastereoselectivity of the hydrogenation reaction of unsaturated aldol **350**. In order to check this hypothesis, *syn*-aldol **350** was subjected to hydrogenation using 17.5 mol% of Wilkinson's catalyst and 5 bar hydrogen gas (see Scheme 161). From analysis of the ^1H NMR spectrum of the crude product it was apparent that aldol **350** had successfully undergone hydrogenation in a similar diastereoselectivity of 56% *d.e.* as that observed previously for hydrogenation of the corresponding aldol **282** derived from the Evans oxazolidin-2-one (60% *d.e.*). The configuration of the major diastereomer was assigned as (2*S*,3*R*,4*R*)-**351a** by consideration of the coupling constant of $J_{(3,4)} = 8.7$ Hz, which was similar to that previously observed for hydrogenation of Evans' aldol **282**, and therefore the same (4*R*)- stereochemistry was assigned. This aldol (4*R*)-**351a** was then purified to > 95% *d.e.* via chromatography, and used as a substrate in subsequent retro-aldol studies.



Scheme 161. Comparison of the hydrogenation reaction of SuperQuat derived aldol **350** with Evans derived aldol **282** using Wilkinson's catalyst

3.6.5 Retro-aldol of SuperQuat derived aldols

Having established that the SuperQuat auxiliary performed well under both the aldol and hydrogenation conditions, it was necessary to demonstrate that aldol **351** would undergo the required retro-aldol reaction. Treatment of aldol **351** with either KHMDS or LHMDS at $-78\text{ }^\circ\text{C}$ and $-40\text{ }^\circ\text{C}$ resulted in no reaction, with no evidence of products arising from either the elimination or retro-aldol reactions (see Table 3.4, entries 1 – 4). This indicated that the *gem*-dimethyl substituents had indeed proven successful in preventing the cyclisation-elimination reaction from occurring, since the corresponding Evans aldol **284** had eliminated cleanly under these conditions. The SuperQuat aldol **351** was therefore subjected to a range of bases, temperatures and solvents in order to find conditions that would enable the retro-aldol reaction to proceed (see Table 3.4).

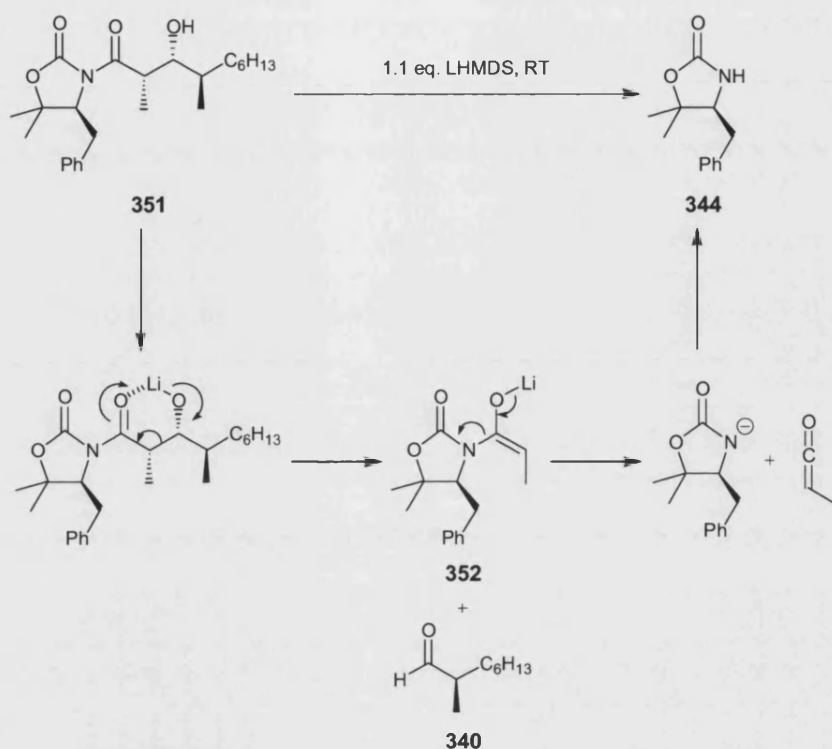


Base ^a	Temperature ^b (°C)	Solvent	Product ratio ^c 351:346:344:340
KHMDS	- 78	THF	no reaction
KHMDS	- 40	THF	no reaction
LHMDS	- 78	THF	no reaction
LHMDS	- 40	THF	no reaction
LHMDS	-15	THF	36 : 27 : 20 : 17
LHMDS	0	THF	0 : 59 : 11 : 30
LHMDS	0	Toluene	0 : 49 : 7 : 44
LHMDS	RT	Toluene	0 : 9 : 85 : 6

^a1.1 equivalents of base; ^bReactions carried out over 2 hours; ^cDetermined by analysis of the ¹H NMR spectrum of the crude product

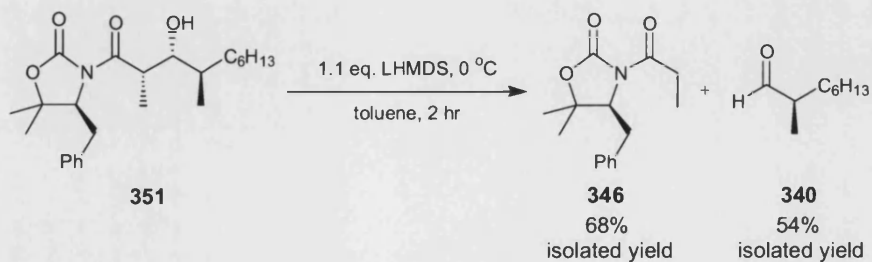
Table 3.4 Anionic retro-aldol reaction of *syn*-aldol **351** under a range of conditions

These results revealed that the yield of aldehyde **340** produced in these anionic retro-aldol reactions was highly dependent on the choice of solvent and temperature employed. Treatment of *syn*-aldol **351** with LHMDS in toluene at room temperature resulted in formation of large amounts of the parent oxazolidin-2-one **344** rather than the desired aldehyde and the *N*-propionyl oxazolidin-2-one **346** (see Table 3.4, entry 8). This was thought to arise from aldol **351** undergoing retro-aldol reaction to afford a lithium enolate **352** that further decomposes via a retro-ketene type mechanism as shown in Scheme 162. Unfortunately, these conditions did not result in any of the desired aldehyde **340** being isolated, however no alternative products could be isolated from an extensive investigation of the aqueous or organic extracts of this reaction.



Scheme 162. Proposed retro-aldol/retro-ketene mechanism for the formation of oxazolidin-2-one **344**

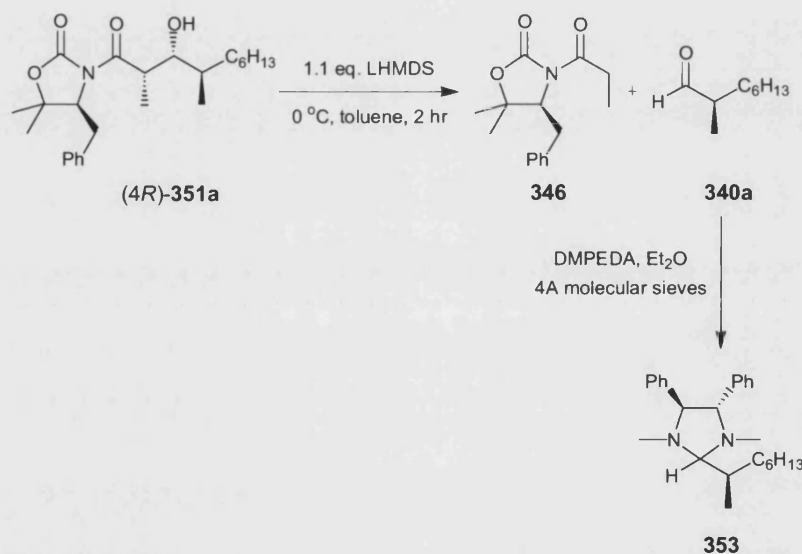
In contrast, cooling the reaction to 0 °C resulted in an improved 44% yield of the desired aldehyde **340** although there was still a small amount of the parent oxazolidin-2-one **344** produced (see Table 3.4, entry 7). However, on decreasing the temperature to - 15 °C the reaction failed to proceed to completion (see Table 3.4, entry 5). Changing the solvent from tetrahydrofuran to toluene resulted in an improved yield of the desired aldehyde **340** and minimised the formation of the SuperQuat oxazolidin-2-one **344**. The retro-aldol reaction was therefore optimised at 0 °C in toluene as this gave a good 44% yield of desired α -methyl aldehyde **340**, 50% yield of *N*-propionyl oxazolidin-2-one **346** and < 6% yield of the parent oxazolidin-2-one **344** (see Scheme 163).



Scheme 163. Optimised retro-aldol conditions of aldol **351**

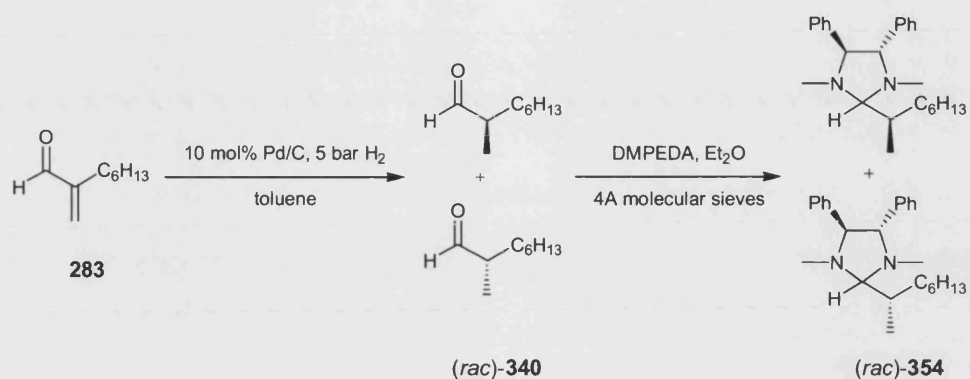
3.7 Determining the enantiomeric excess of α -methyl octanal **340**

Since I had discovered conditions that enabled the retro-aldol reaction to proceed in good yield it was then necessary to determine whether the basic reaction conditions employed for cleavage had resulted in racemisation of the α -stereocentre of chiral aldehyde **340**. Alexakis *et al.* had shown that derivatisation of racemic chiral aldehydes with enantiomerically pure (*S,S*)-*N,N'*-dimethyl-1,2-diphenyl ethylene diamine (DMPEDA) afforded imidazolidinone diastereomers whose ^1H NMR spectra were well resolved, thus enabling the enantiopurity of the starting aldehydes to be determined by integration of appropriate resonances.^[209] Therefore, diastereomerically pure aldol (*4R*)-**351a** was subjected to the optimised retro-aldol procedure using LHMDS in toluene at 0 °C which gave a crude reaction product which was evaporated *in vacuo* and redissolved in ether before addition of an excess of DMPEDA to afford the derivatised product **353** without resolution (see Scheme 164).



Scheme 164. Derivatisation of chiral aldehyde **340a** using DMPEDA

An authentic sample of racemic aldehyde **340** was prepared via hydrogenation of unsaturated aldehyde **283** with 10 mol% palladium on carbon, which was then derivatised with DMPEDA to afford a 50:50 mixture of diastereomers **354** whose ^1H NMR was acquired for comparative purposes (see Scheme 165).



Scheme 165. Derivatisation of racemic aldehyde **340** using DMPEDA

The ^1H NMR spectrum of the imidazolidine derived from the racemic aldehyde showed a series of doublets between 3.5 and 4.2 ppm corresponding to the resonances of the PhCH and N_2CH protons of both diastereomers as shown in Figure 8.

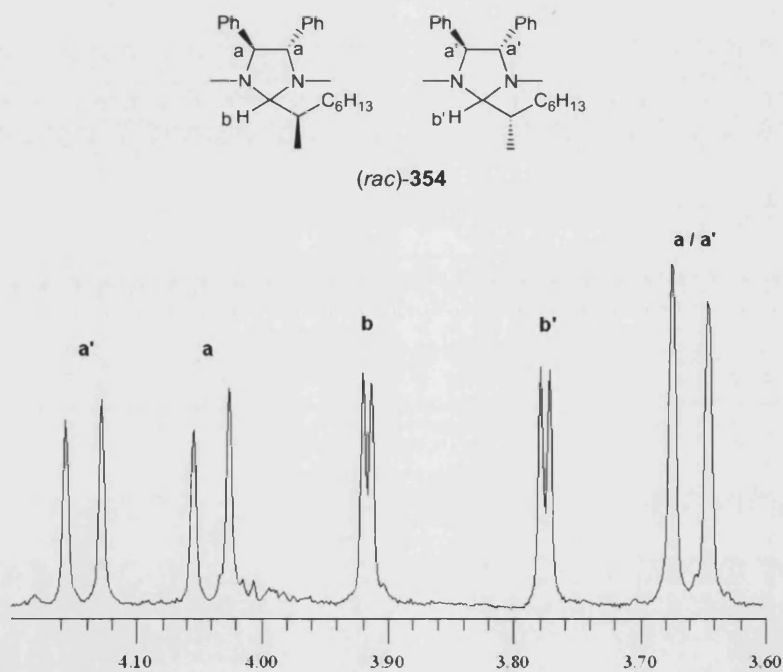


Figure 8. ^1H NMR spectrum of racemic aldehyde derivatised with DMPEDA

Integration of these ^1H NMR resonances of the mixture of diastereomeric imidazolidines derived from α -methyl aldehyde **340a** produced in the retro-aldol cleavage of

diastereomerically pure aldol (4*R*)-**351a** revealed that less than 5% racemisation had occurred (see Figure 9). This was considered to be acceptable, especially as these chiral α -methyl aldehydes were subsequently shown to be highly susceptible to racemisation.

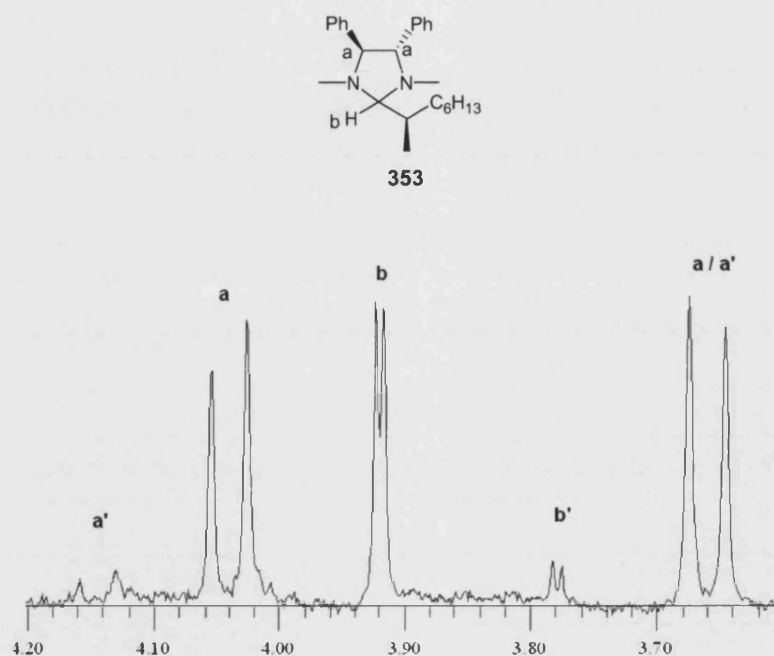


Figure 9. ^1H NMR spectrum of aldehyde **340a** from anionic retro-aldol reaction of aldol (4*R*)-**351a** derivatised with DMPEDA

Although the anionic retro-aldol reaction was shown not to erode the enantiomeric excess of the chiral aldehyde significantly, it proved very difficult to isolate without any further racemisation. Purification of the crude reaction mixture by distillation or chromatography over silica or alumina resulted in an erosion of the enantiomeric excess of aldehyde **340a** to 70 – 83% *e.e.*, as shown by the DMPEDA derivatisation protocol. The aldehyde also proved labile to racemisation after leaving on the bench for a few days. This issue was solved by derivatising the chiral aldehyde *in situ* to afford stable chiral products as described in the next chapter.

3.8 Conclusions

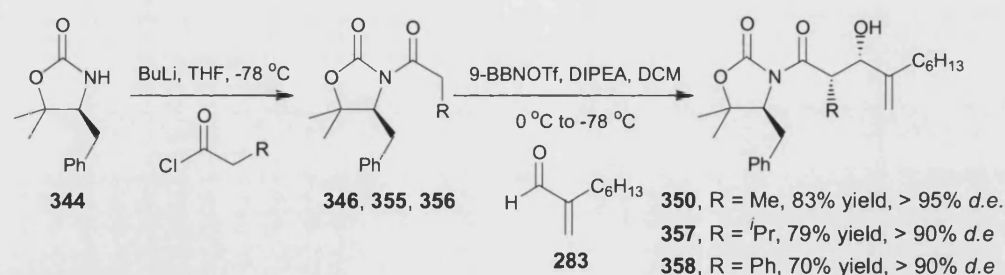
Having found appropriate conditions for the retro-aldol reaction our novel aldol/directed reaction/retro-aldol methodology could be considered to be validated. Optimisation of the hydrogenation procedure was then necessary and this will be discussed in the next chapter.

Chapter 4: Optimisation of the hydrogenation reaction

Having established successful *syn*-aldol and retro-aldol conditions for SuperQuat derived substrates it was important to see whether our hydrogenation reactions could be improved to give higher levels of diastereoselectivity.

4.1 Effect of α -substituents on hydrogenation with Wilkinson's catalyst

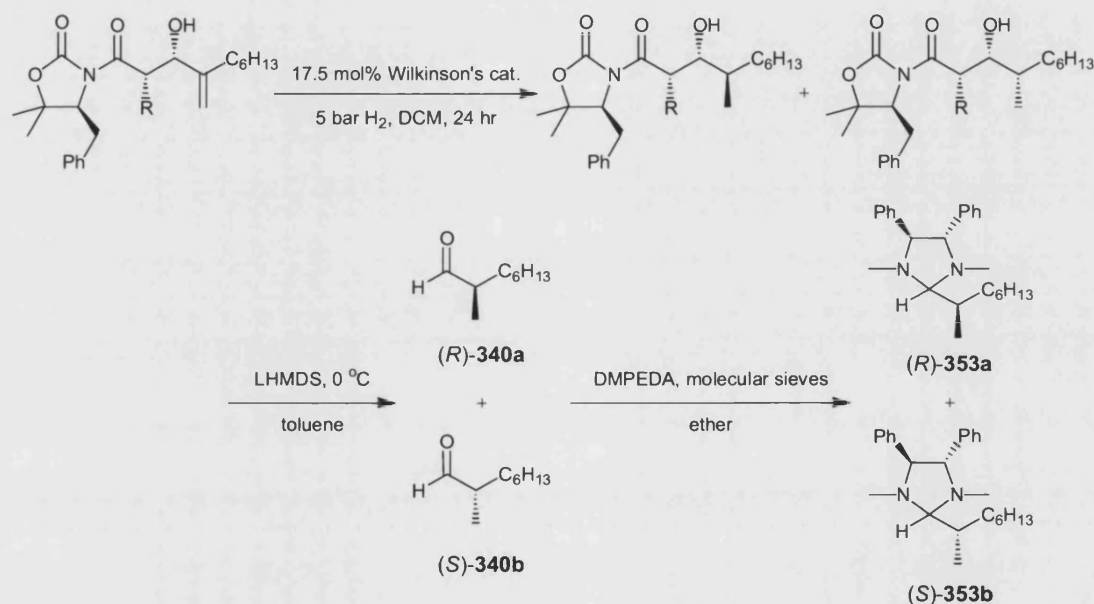
The observation that hydrogenation of the isomerised Evans aldol **285** with Wilkinson's catalyst gave the same major diastereomer as hydrogenation of methylene-aldol **282**, rather than the opposite diastereomer as predicted from allylic strain models lead us to postulate that for this catalyst the steric environment around the alkene might be more important in governing diastereoselectivity than the directing effect of the hydroxyl group. In order to investigate these hydrogenation reactions further, unsaturated aldols **350** and **357** – **358** containing three different substituents at their α -positions were synthesised according to our established procedures. Therefore, SuperQuat auxiliary **344** was deprotonated with butyl lithium in THF at $-78\text{ }^{\circ}\text{C}$ and acylated with the appropriate acid chloride to afford *N*-acylated auxiliaries **346** and **355** – **356**, followed by *syn*-aldol reaction using unsaturated aldehyde **283**, 9-BBNOTf and diisopropylethylamine to yield *syn*-aldols **350** and **357** – **358** in reasonable yield and good diastereoselectivity (see Scheme 166).



Scheme 166. Synthesis of unsaturated aldols **350**, **357**, **358**

These unsaturated aldols **350** and **357** – **358** were then subjected to hydrogenation reactions using 17.5 mol% Wilkinson's catalyst and 5 bar hydrogen pressure as shown in

Table 4.1. The diastereomeric excess of these reactions was difficult to determine by ^1H NMR spectroscopy due to multiple overlapping peaks. Therefore, in order to determine the diastereoselectivity and configuration of the major products, the crude reaction product from each hydrogenation reaction was treated with LHMDS at $0\text{ }^\circ\text{C}$, resulting in clean retro-aldol reactions in each case. Immediate derivatisation of aldehyde **340** produced in these retro-aldol cleavage reactions with DMPEDA allowed the enantiomeric excess of the chiral aldehyde to be determined by analysis of the ^1H NMR spectra of the resultant mixture of diastereomeric imidazolidines. The absolute configuration of the aldehyde could also be determined by comparison with the spectra arising from derivatisation of the enantiomerically enriched (*R*)-aldehyde **340a** produced earlier.



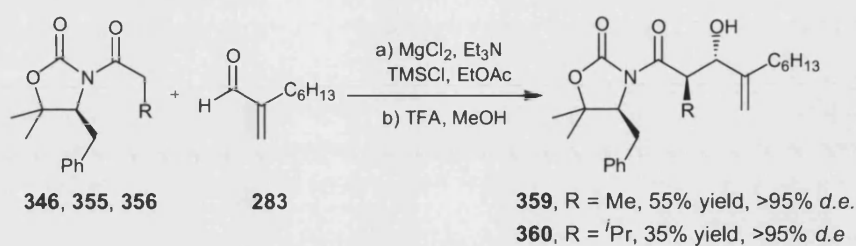
Aldol	R	<i>e.e.</i> ^a (%)	Stereochemistry of major aldehyde
350	Me	60	<i>R</i>
357	<i>i</i> Pr	52	<i>S</i>
358	Ph	62	<i>S</i>

^a Determined by derivatisation with DMPEDA

Table 4.1 Hydrogenation of aldols **350**, **357**, **358** with Wilkinson's catalyst

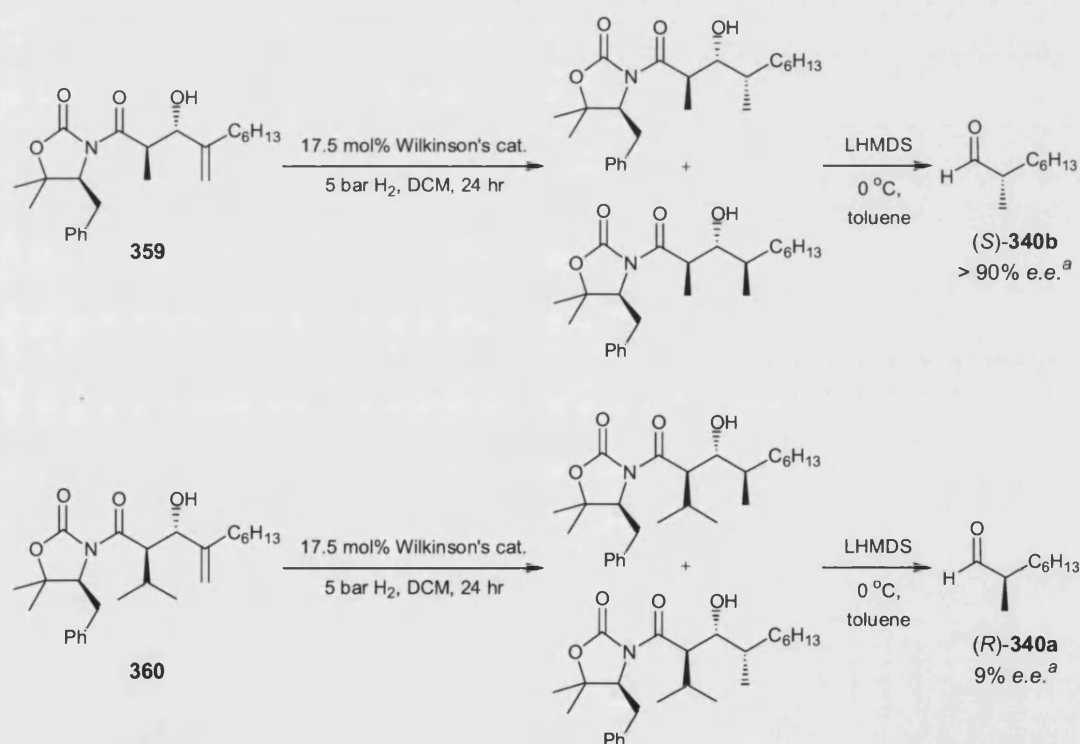
Remarkably, it was found that increasing the steric bulk of the substituent at the α -position from a methyl group to an isopropyl group in aldol **357** not only reduced the diastereoselectivity of the hydrogenation reaction, but also reversed the facial selectivity affording the opposite diastereomer with a (4*S*)-configuration. Aldol **358** containing a phenyl group in the α -position was also reduced with poorer diastereocontrol, once again resulting in inversion of configuration in favour of the (*S*)-enantiomer of product.

In order to further investigate the effect of the α -substituent we decided to change the relative stereochemistry at the α - and β -positions of the aldol substrate from *syn* to *anti*. Therefore, *N*-acylated auxiliaries **346**, **355** and **356** were dissolved in ethyl acetate before addition of magnesium chloride, triethylamine, chlorotrimethylsilane and the unsaturated aldehyde **283** according to Evans' recently published procedure (see Scheme 167).^[185] The mixture was stirred at room temperature before filtering and treatment with trifluoroacetic acid in methanol to remove the *O*-trimethylsilyl group. These *anti*-aldol reactions tended to be very slow, with the *N*-propionyl auxiliary **346** proceeding to 60% conversion after 24 hours, and the *N*-isovaleryl auxiliary **355** affording 40% conversion after 72 hours. However the diastereoselectivity of these reactions was high and therefore the diastereomerically pure material could easily be isolated after column chromatography albeit in low yield. Evans *et al.* have reported that the addition of 30mol% of NaSbF₆ improves the conversion in this reaction but this was not attempted as sufficient aldol substrate was isolated from these reactions to carry out our desired hydrogenation reactions. For the *N*-phenylacetyl oxazolidin-2-one **356** the ¹H NMR spectrum of the crude product after 24 hours was very complex, and although the ¹H NMR spectrum revealed the formation of some of the desired product, it was very difficult to isolate by column chromatography. The stereochemistry of aldol products **359** and **360** was assigned according to literature precedent with a larger coupling constant of $J_{(2,3)} = 10.0$ Hz (**360** used as an example) observed for the vicinal protons characteristic of an *anti*-aldol having been formed ($J_{(2,3)} = 4.8$ Hz for corresponding *syn*-aldol).



Scheme 167. Synthesis of *anti*-aldols **359** and **360**

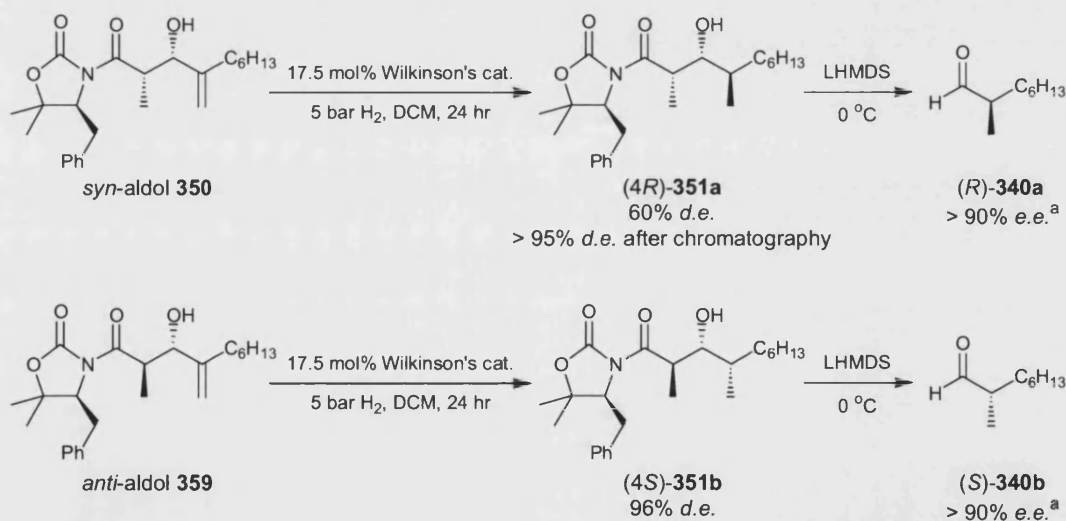
Anti-aldols **359** and **360** were then subjected to hydrogenation reaction with 17.5 mol% of Wilkinson's catalyst under 5 bar hydrogen pressure. 1.1 equivalents of LHMDS were then added to the crude product in toluene at 0 °C to affect the retro-aldol reaction before derivatisation with DMPEDA to determine the enantiomeric excess and stereochemistry of the resultant aldehyde as described previously (see Scheme 168).



Scheme 168. Hydrogenation of *anti*-aldols **359** and **360** with Wilkinson's catalyst (^a determined by derivatisation with DMPEDA)

Analysis of the ^1H NMR spectrum of the crude product arising from hydrogenation of the α -methyl-substituted *anti*-aldol **359** showed very high levels of diastereoselectivity (96% *d.e.* by integration) for an (*S*)-configuration at the newly formed stereocentre. However, increasing the steric bulk at the α -position to an isopropyl group in *anti*-aldol **360** led to complete loss of selectivity in the hydrogenation reaction affording an essentially 1:1 mixture of the two diastereomers.

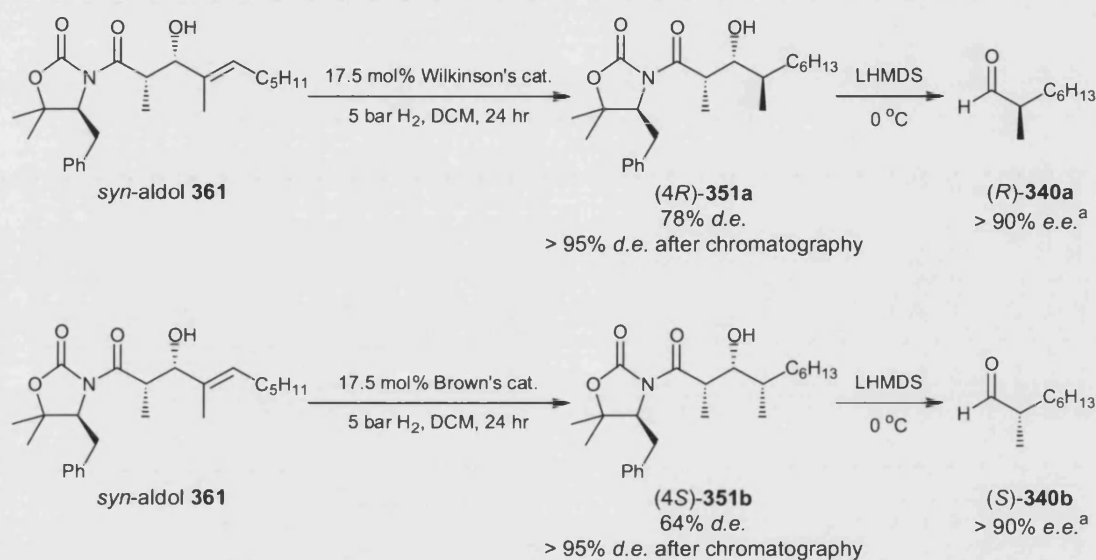
The result for α -methyl *anti*-aldol **359** was very promising as it would allow for substrate controlled hydrogenation protocols where both enantiomers of chiral aldehyde **340** could be accessed with good selectivity depending on whether a *syn*- or *anti*-aldol was employed as a substrate (see Scheme 169). Therefore, hydrogenation of *syn*-aldol **350** with Wilkinson's catalyst affords the (*4R*)-aldol product **351a** in 60% *d.e.*, which could be purified to greater than 95% *d.e.* via chromatography, before retro-aldol cleavage to afford (*R*)-aldehyde **340a** in greater than 90% *e.e.* Alternatively, hydrogenation of *anti*-aldol **359** with Wilkinson's catalyst affords the (*4S*)-aldol product **351b** in 96% *d.e.*, which after retro-aldol cleavage affords the opposing (*S*)-aldehyde **340b** in greater than 90% *e.e.*



Scheme 169. Substrate controlled hydrogenation using Wilkinson's catalyst (^a determined by derivatisation with DMPEDA)

These results complement our earlier screening results which employed catalyst controlled diastereocontrol to afford either enantiomer of the target aldehyde (see Scheme 170).

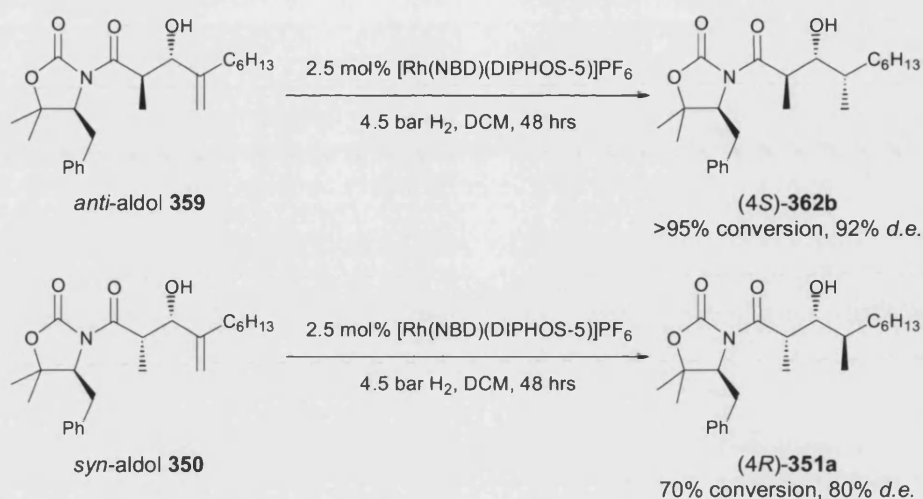
Therefore we demonstrated that hydrogenation of *syn*-aldol **361** with Wilkinson's catalyst afforded the (4*R*)-aldol **351a** in 78% *d.e.*, which could be purified to homogeneity and subjected to retro-aldol reaction to afford (*R*)-aldehyde **340a** in greater than 90% *e.e.* Conversely, hydrogenation with Brown's catalyst afforded the (4*S*)-aldol **351b** in 64% *d.e.* which after purification and retro-aldol reaction afforded (*S*)-aldehyde **340b** in greater than 90% *e.e.*



Scheme 170. Catalyst controlled hydrogenation of *syn*-aldol **361** (^a determined by derivatisation with DMPEDA)

4.2 Hydrogenation of *anti*-aldols with Brown's catalyst

Hydrogenation of α -methyl *anti*-aldol **359** was also attempted using Brown's catalyst [Rh(NBD)(DIPHOS-5)]PF₆. The most successful conditions previously established using Brown's catalyst employed 2.5 mol% catalyst loading, 4.5 bar hydrogen over 48 hours, therefore these conditions were used for the hydrogenation of *anti*-aldol **359** as shown in Scheme 171.

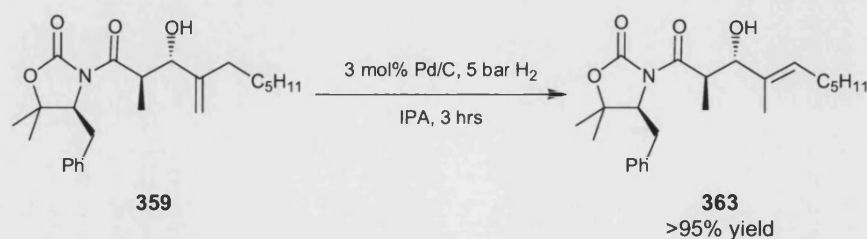


Scheme 171. Hydrogenation of *anti*-aldol **359** and *syn*-aldol **350** with Brown's catalyst

Analysis of the ^1H NMR spectrum of the crude product showed that this hydrogenation reaction proceeded with high diastereoselectivity (92% *d.e.* by integration). Comparison with the ^1H NMR spectrum obtained from hydrogenation of *anti*-aldol **359** previously produced using Wilkinson's catalyst (see Scheme 168) showed that the same major (4*S*)-diastereomer **362b** had been produced.

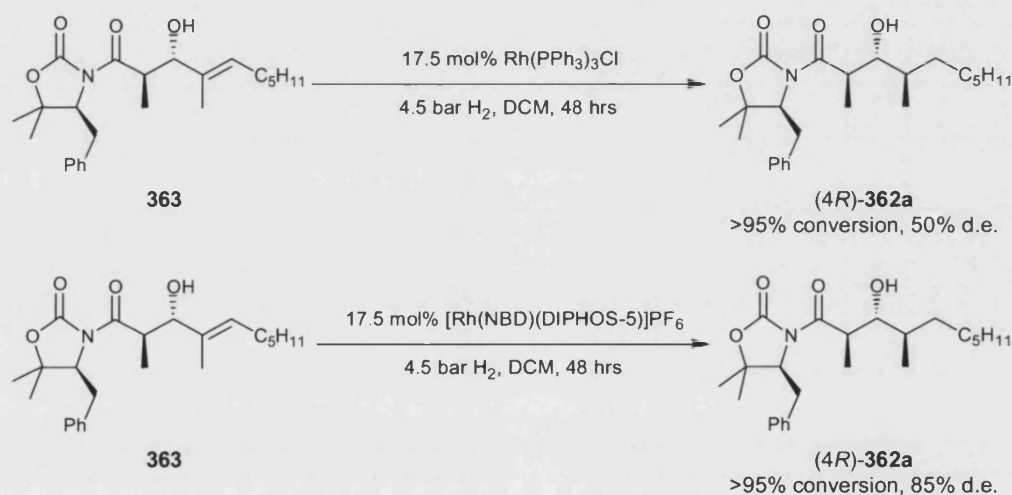
4.3 Hydrogenation of isomerised *anti*-aldols

For completeness it was interesting to see what effect changing the stereochemistry at the α -position had on hydrogenation of the tri-substituted alkene functionality of aldol **363**. α -Methyl substituted *anti*-aldol **359** in IPA was treated with palladium on carbon under 5 bar hydrogen for 3 hours to afford the isomerised *anti*-aldol **363** in almost quantitative yield (see Scheme 172).



Scheme 172. Synthesis of isomerised *anti*-aldol **363**

Isomerised *anti*-aldol **363** was then subjected to hydrogenation with both Brown's and Wilkinson's catalyst at 17.5 mol% and 4.5 bar hydrogen (see Scheme 173). Comparison of the ^1H NMR spectra obtained from these reactions with authentic standards (see Scheme 168) showed that the major diastereomer formed in both these reactions was the (4*R*)-diastereomer **362a**. This is what would have been expected from an allylic strain model where changing from a 1,1-substituted olefin to a 1,2-substituted olefin would be predicted to give the opposite diastereomer of product (see Chapter 1). Interestingly, Wilkinson's and Brown's catalysts both favour the same diastereomer, which was not observed for hydrogenation of the isomerised *syn*-aldol **285**. This suggests therefore that for the *anti*-aldol there may be 'matching' between the hydroxyl directing effect and the steric effect, which leads to good (4*R*)-selectivity.



Scheme 173. Hydrogenation reaction of isomerised *anti*-aldol **363**

In my hands Brown's catalyst was found to be very sensitive to exposure to the atmosphere and therefore great care had to be taken to ensure that hydrogenation reactions were carried out in a completely inert atmosphere, with several experiments failing under less rigorous conditions. In contrast, Wilkinson's catalyst was much more robust and cheaper,^[210] and therefore we consider it to currently be the catalyst of choice for these hydrogenation reactions.

4.4 Rationalising the diastereoselectivity of hydrogenation reactions

Although hydrogenation reactions of *syn*-aldols **350** and **361** and *anti*-aldols **359** and **363** had proceeded with good levels of diastereocontrol with Brown's and Wilkinson's catalysts it was clear that the major isomer produced was not always the expected one. The major isomer produced in each of these reactions is summarised in Table 4.2 (Brown's catalyst) and Table 4.3 (Wilkinson's catalyst).

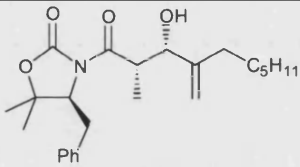
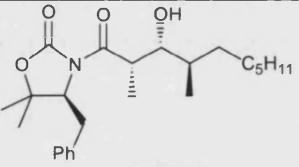
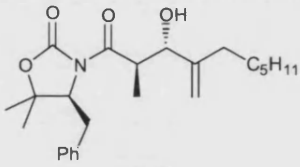
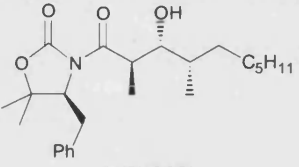
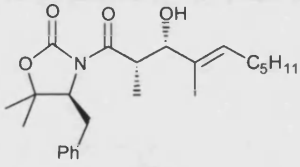
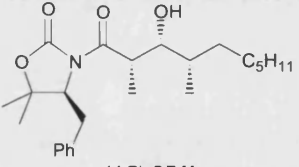
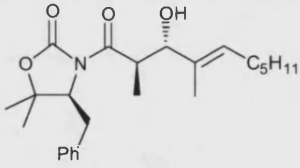
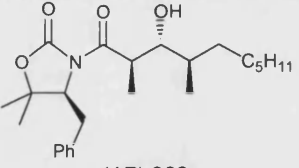
Aldol	Major diastereomer	<i>d.e.</i>
 <p>350</p>	 <p>(4<i>R</i>)-351a</p>	80%
 <p>359</p>	 <p>(4<i>S</i>)-362b</p>	92%
 <p>361</p>	 <p>(4<i>S</i>)-351b</p>	64%
 <p>363</p>	 <p>(4<i>R</i>)-362a</p>	85%

Table 4.2 Major diastereomer produced in hydrogenation reactions using Brown's catalyst

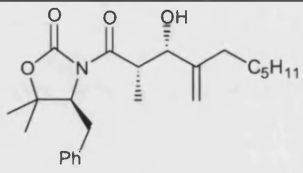
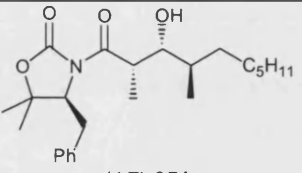
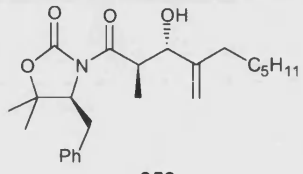
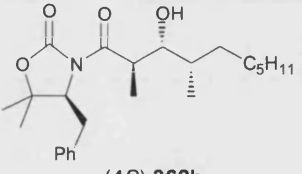
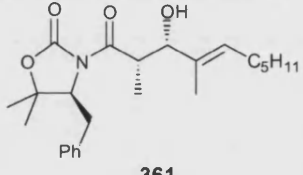
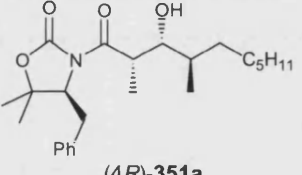
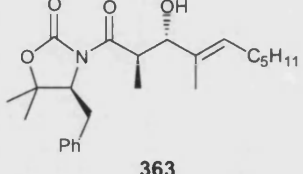
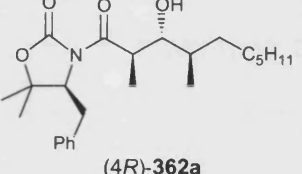
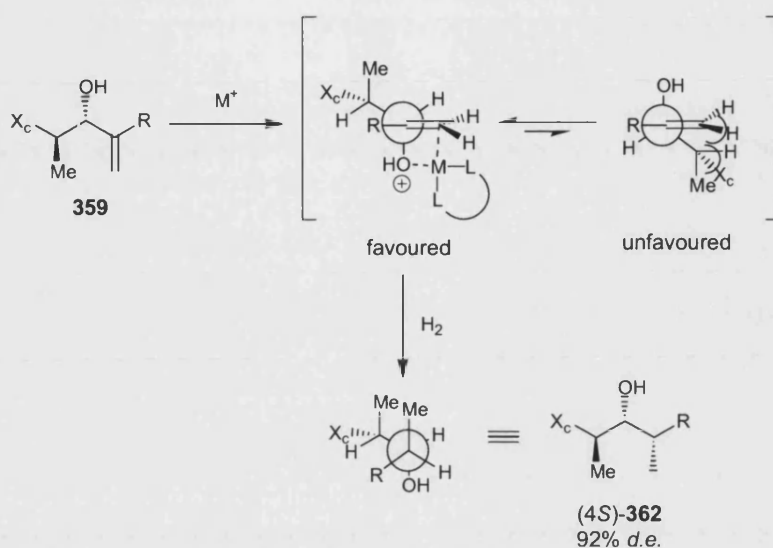
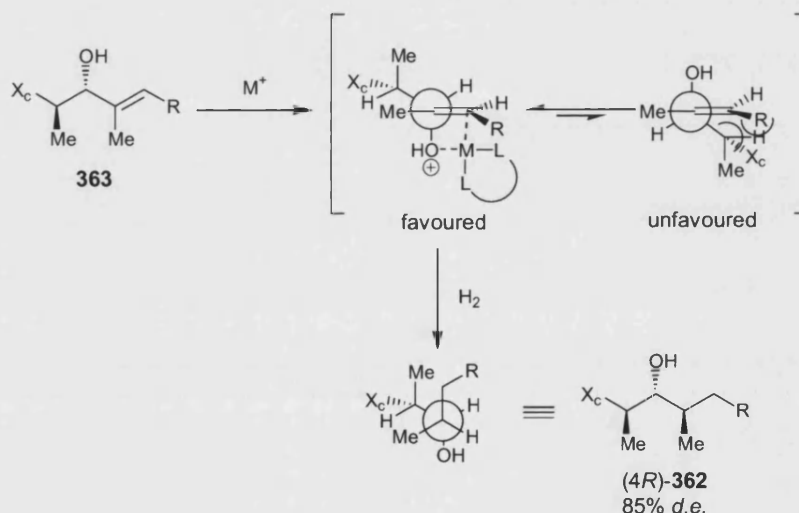
Aldol	Major diastereomer	d.e.
 350	 (4R)-351a	60%
 359	 (4S)-362b	96%
 361	 (4R)-351a	78%
 363	 (4R)-362a	50%

Table 4.3 Major diastereomer produced in hydrogenation reactions using Wilkinson's catalyst

For Brown's catalyst it appears that the configuration at the α -position is important in determining the diastereoselectivity of the hydrogenation reaction. It is proposed that this is because the steric demand of the methyl group is important in determining which conformer is favoured in the allylic strain model. For the *syn*-aldols **350** and **361** this steric interaction matches the simple allylic strain model as described in Chapter 1 to produce the expected major diastereomers observed by Evans *et al.*^[170] For the *anti*-isomers **359** and **363** the opposite diastereomers are produced due to minimisation of steric interactions as shown in Scheme 174 and Scheme 175.



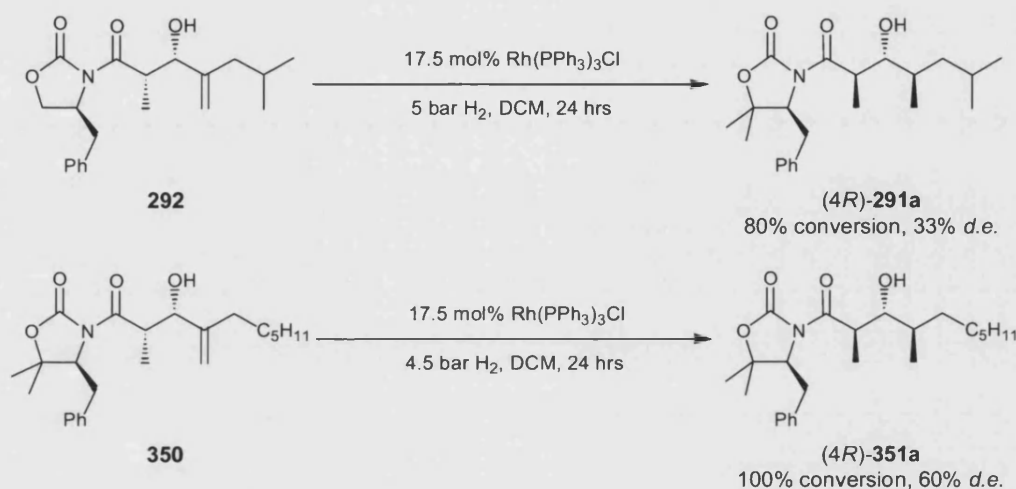
Scheme 174. Minimisation of steric interactions in hydrogenation of *anti*-aldol **359** with Brown's catalyst



Scheme 175. Minimisation of steric interactions in hydrogenation of isomerised *anti*-aldol **363** with Brown's catalyst

In the case of Wilkinson's catalyst both the 1,1-substituted *syn*-aldol **350** and the 1,2-substituted *syn*-aldol **361** give the same product unlike the reactions with Brown's catalyst. This suggests that hydrogenation reactions with this catalyst may not be directed by the hydroxyl functionality in the same way as Brown's. Indeed it is unlikely that the Wilkinson's catalyst complex contains two labile ligands that would allow it to coordinate to both the hydroxyl group and the olefin at the same time. In this case it is postulated that

the diastereoselectivity observed in these reactions is solely dependent on the conformation of the substrate molecule, with a number of low energy conformers all contributing to the diastereocontrol. This hypothesis is supported by the large decrease in diastereoselectivity that was observed when *syn*-aldol **292** was used in the hydrogenation reaction with Wilkinson's catalyst (see Scheme 176). It can be seen that a small change in the alkyl chain β - to the alkene functionality had a large effect on the diastereoselectivity even though the local environment around the allylic alcohol fragment had not changed.



Scheme 176. Comparison of diastereoselectivity of hydrogenation of *syn*-aldols **292** and **350** using Wilkinson's catalyst

Some molecular modelling calculations were carried out on our aldol substrates (C_3H_7 chain used in place of C_6H_{13} for ease of calculation) in order to determine the likely lowest energy conformation using Spartan 04. Structures were optimised *in vacuo* before application of the PM3HD (hexadecane) solvation system. It was thought that the presence of a hydrogen bond between the hydroxyl group and the *exocyclic* carbonyl would be important in determining the lowest energy conformation of the substrate aldol. Interestingly it was found that the predicted lowest energy conformations for the α -methyl *syn*-aldol **350** showed the presence of this hydrogen bond (see Figure 10). However, altering the configuration at the α -position to α -methyl *anti*-aldol **359** or increasing the steric bulk at the α -position to α -isopropyl-substituted *syn*-aldol **357**, resulted in the predicted low energy conformer no longer containing a hydrogen bond (see Figure 11 and Figure 12). Examination of these structures highlights how critical the steric environment

of the substrate, and the presence or absence of a hydrogen bond is in governing the orientation of the alkene fragment. It is likely that there are multiple low energy states that all contribute to the diastereoselectivity of these hydrogenation reactions and therefore levels of diastereocontrol are difficult to predict or rationalise. The importance of the hydrogen bond is also supported by the result of the solvent screen carried out on hydrogenation of *syn*-aldol **282** since the use of Wilkinson's catalyst in polar protic solvents such as ethanol drastically reduced the diastereoselectivity of the reaction, probably by disrupting the hydrogen bonding within the molecule (see Table 2.5).

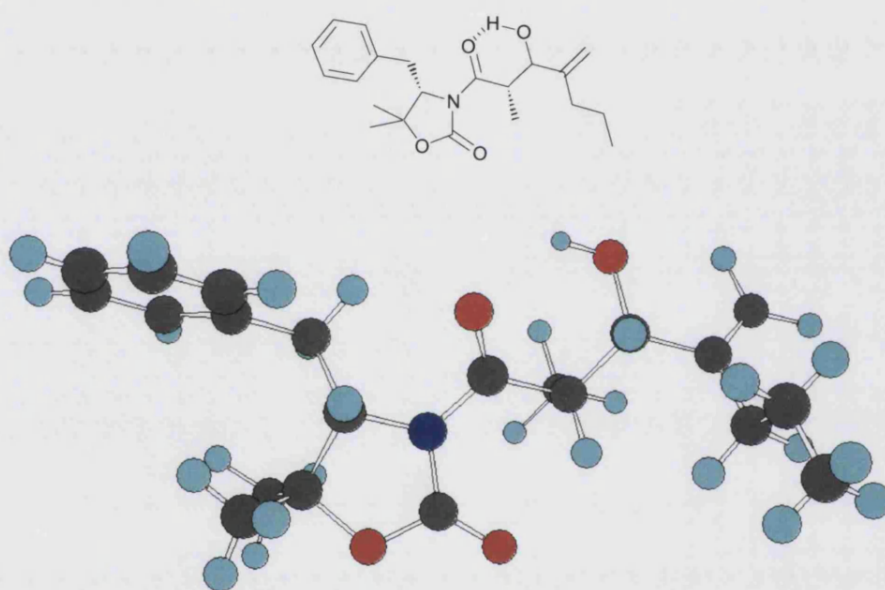


Figure 10. Low energy model for α -methyl *syn*-aldol **350**

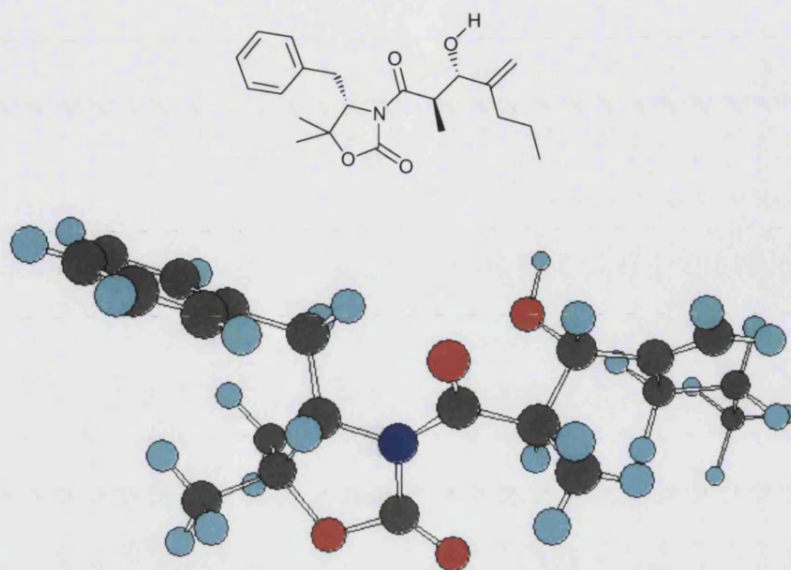


Figure 11. Low energy model for α -methyl *anti*-aldol 359

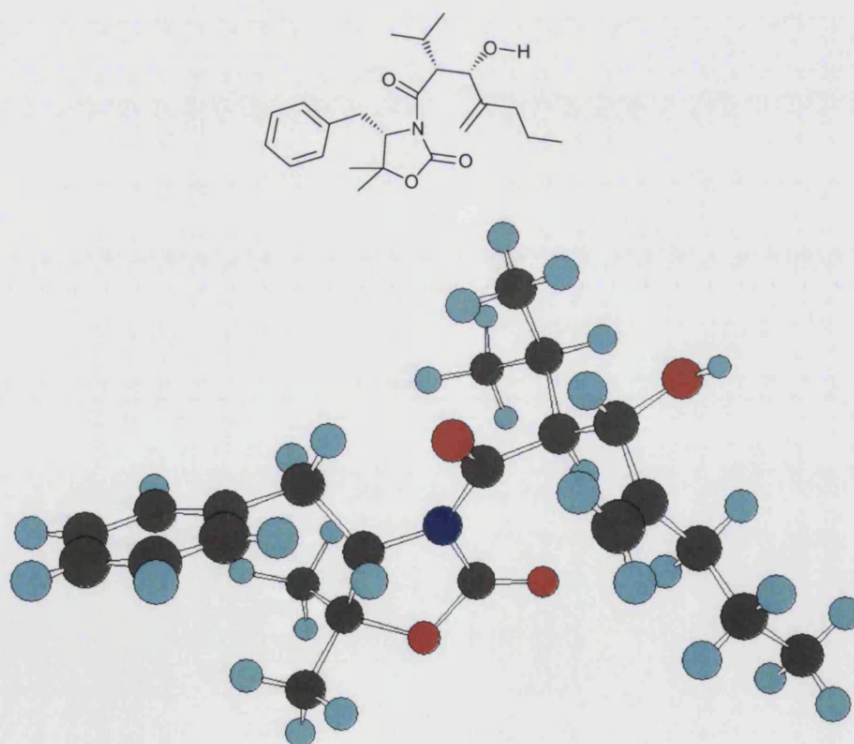
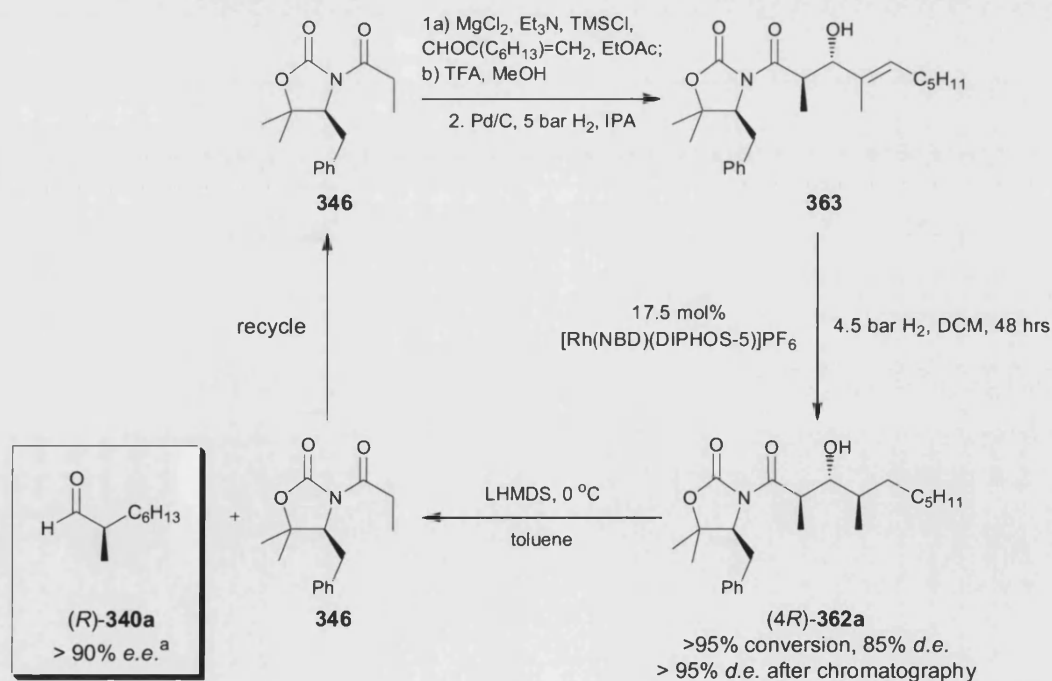


Figure 12. Low energy model for α -isopropyl *syn*-aldol 357

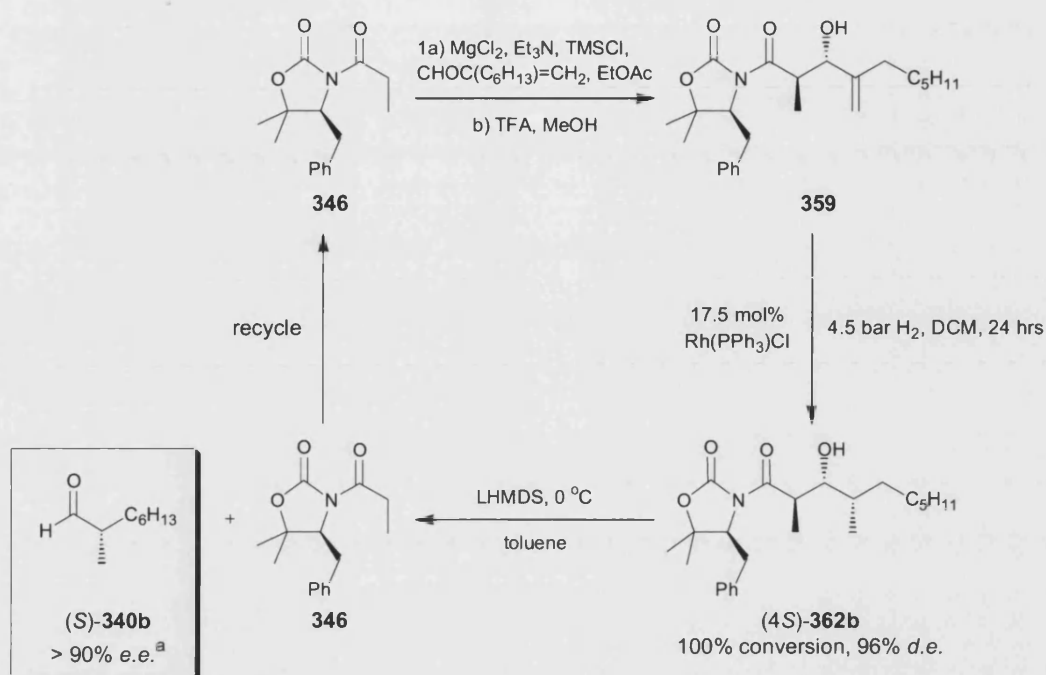
The results of the molecular modelling suggest that small changes in sterics or stereochemistry of the substrate molecule can have a large effect on its conformation and therefore the transition states and outcomes of the hydrogenation reaction with Wilkinson's catalyst are likely to be substrate specific and difficult to predict.

4.5 Optimised retro-aldol reactions

It can be seen that our hydrogenation strategy had proven successful in affording protocols for the synthesis of both enantiomers of chiral aldehyde using our originally envisaged aldol/hydrogenation/*retro*-aldol protocol, with the most successful hydrogenation reactions using *anti*-aldol substrates **363** and **359** described in Scheme 177 and Scheme 178. Therefore, *anti*-aldols **363** and **359** could be hydrogenated with either Browns catalyst or Wilkinson's catalyst to afford either aldol diastereomer (4*R*)-**362a** and (4*S*)-**362b** in high *d.e.* Subsequent treatment of each reduced aldol product (4*R*)-**362a** and (4*S*)-**362b** with LHMDs at 0 °C initiated the *retro*-aldol reaction enabling access to both enantiomers of chiral aldehyde (*R*)-**340a** and (*S*)-**340b** in good yield and greater than 90% *e.e.*



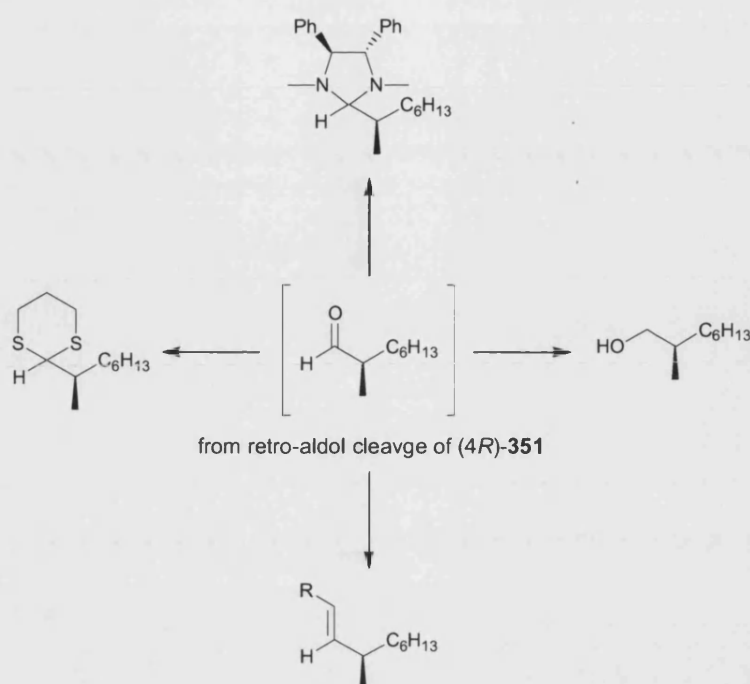
Scheme 177. Optimal synthesis of (*R*)-enantiomer of aldehyde **340** using our aldol/hydrogenation/retro-aldol strategy (^a determined by derivatisation with DMPEDA)



Scheme 178. Optimal synthesis of (*S*)-enantiomer of aldehyde **340** using our aldol/hydrogenation/retro-aldol strategy (^a determined by derivatisation with DMPEDA)

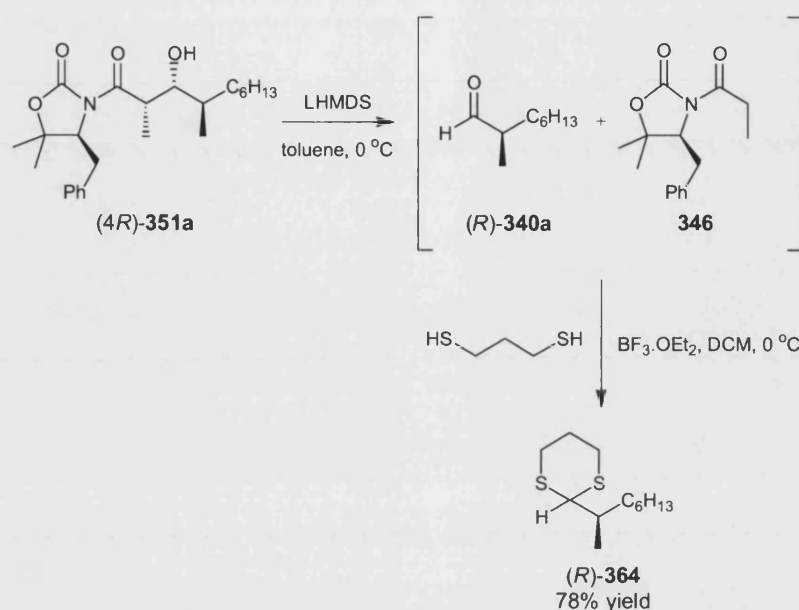
4.6 *In situ* derivatisation of α -substituted aldehyde **340**

Although chiral aldehyde **340** was shown not to racemise significantly during the retro-aldol cleavage reaction it proved difficult to isolate the aldehyde in an enantiomerically pure form unless great care was taken. To overcome this problem it was decided that it would be useful to devise protocols that would enable the chiral aldehyde to be derivatised *in situ* to form a range of synthetically useful chiral synthons that would be less susceptible to epimerisation at the chiral centre (see Scheme 179).



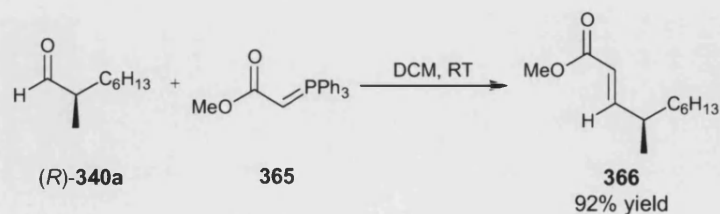
Scheme 179. Possible derivatisation of chiral aldehyde **340** to synthesise other chiral synthons

As described previously, derivatisation of chiral aldehyde **340** with DMPEDA forms a stable chiral imidazolidine.^[209] In a similar way, diastereomerically pure aldol (4*R*)-**351a** was treated with LHMDS in toluene at 0 °C which underwent retro-aldol cleavage to afford chiral aldehyde (*R*)-**340a**. The solvent was evaporated *in vacuo* and the crude product redissolved in DCM and immediately treated with propane-1,3-dithiol and boron trifluoride diethyl etherate (see Scheme 180) according to the procedure previously reported by Jones *et al.*^[211] Purification by column chromatography allowed isolation of the desired dithiane product (*R*)-**364** in good yield, whose specific rotation was found to be + 8.0 ° (*c* = 3, ether), which compared well with the previously reported literature value for this enantiomerically pure dithiane of + 8.3 ° (*c* = 3, ether).^[212] This indicates that the α -stereocentre is not racemised in the retro-aldol/derivatisation protocol whilst providing further evidence that the absolute configuration of the α -methyl centre of the aldehyde was indeed (*R*) ($[\alpha]_D^{25}$ - 9.6 ° for (*S*)-enantiomer, *c* = 3, ethanol).^[212]



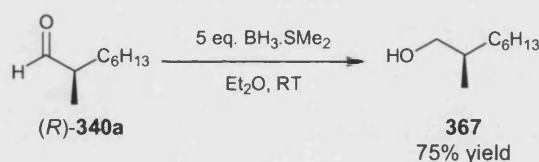
Scheme 180. Synthesis of (*R*)-dithiane **364**

In the same way, the crude chiral aldehyde (*R*)-**340a** from the retro-aldol reaction of (*4R*)-**351a** was reacted with the stabilised ylid **365** to produce the chiral (*R*)- α,β -unsaturated ester **366** in excellent yield after column chromatography (see Scheme 181). Although (*R*)- α,β -unsaturated ester **366** is not reported in the literature, this type of Wittig reaction has been carried out previously on a number of structurally related chiral alkyl aldehydes, and in all cases the reaction was found to proceed with no loss of enantiopurity.^[213-215] Also, the specific rotation of (*E*)-(*R*)-4-methyl-dec-2-enoic acid methyl ester **366** was found to be -27.5° (c 0.40, CHCl_3), which compared well to the previously reported literature value for the structurally similar enantiomerically pure (*E*)-(*R*)-4-methyl-oct-2-enoic acid ethyl ester of -30.8° (c 1.0, CHCl_3).^[216]



Scheme 181. Synthesis of α,β -unsaturated ester (*R*)-**366**

Enders and Schüßeler previously reported reduction of aldehyde (*S*)-**340b** using a borane dimethyl sulfide complex in their RAMP/SAMP hydrazone mediated synthesis of the female pheromone components of the spring hemlock looper and the pitch pine looper.^[217] Gas chromatography over a chiral stationary phase indicated that under these conditions there was no detectable racemisation of the chiral centre. In the same way, chiral aldehyde (*R*)-**340a** from the crude retro-aldol reaction of (*4R*)-**351a** was treated with an excess of borane dimethyl sulfide to yield chiral alcohol **367** in good yield (see Scheme 182). The specific rotation of alcohol (*R*)-**367** was found to be + 10.0 ° (c 1.0, CHCl₃) which corresponded very well with the literature value for the enantiomerically pure compound + 10.3 ° (c 1.0, CH₂Cl₂),^[218] indicating that the α-methyl stereocentre had not racemised.



Scheme 182. Synthesis of chiral alcohol (*R*)-**367**

It can therefore be seen that it is possible to derivatise the chiral aldehyde formed from our novel aldol/ hydrogenation/retro-aldol strategy into a number of enantiomerically enriched, stable chiral synthons which would prove to be synthetically useful.

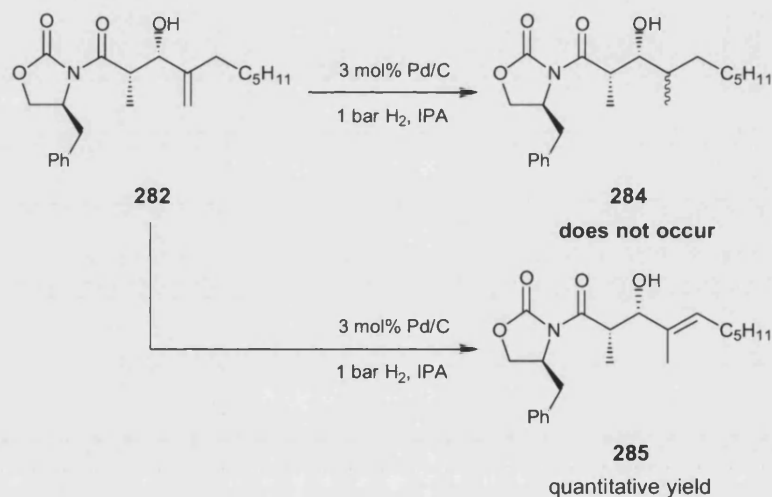
4.7 Conclusions

It has been demonstrated that our aldol/hydrogenation/retro-aldol protocol could be used for the stereodivergent synthesis of both enantiomers of chiral α-methyl aldehyde **340** which could subsequently be easily derivatised *in situ* to afford synthetically useful chiral synthons in an enantiomerically pure form.

Chapter 5: Investigations into palladium on carbon isomerisation reaction

5.1 Introduction

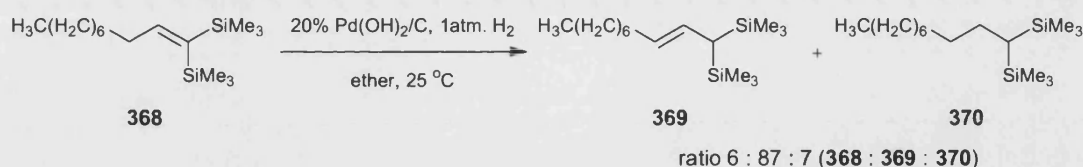
As described in Chapter 2 during the initial screen of hydrogenation reactions, attempted hydrogenation of unsaturated aldol **282** with 3 mol% palladium on carbon under 1 bar hydrogen pressure resulted in the unexpected formation of isomerised aldol product **285** in essentially quantitative yield as shown in Scheme 183.



Scheme 183. Observed isomerisation of aldol **282** using palladium on carbon as a catalyst

It is suspected that this type of isomerisation pathway may also be present in some of the other hydrogenation reactions described in this thesis (see Chapter 2), however these isomerisation products are not observed as the hydrogenation reaction proceeds to afford the fully reduced product **284**. Isomerisations of allylic alcohols to enolates have been reported previously using rhodium catalysts,^[219,220] whilst Hodgson *et al.* have reported the isomerisation of vinylidisilane **368** to allyldisilane **369** using palladium on carbon (see Scheme 184).^[221] However, I could find no literature precedent for isomerisations of allylic methylenic alcohols with palladium and it was therefore decided to carry out further

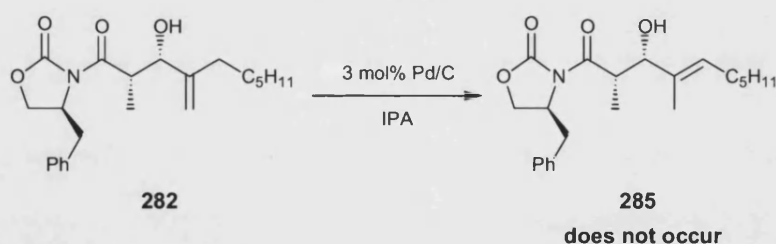
investigations to see if more information could be elucidated about the mechanism of this reaction.



Scheme 184. Palladium catalysed isomerisation of vinyldisilane **368** to afford allyldisilane **369**

5.2 Effect of hydrogen pressure on isomerisation

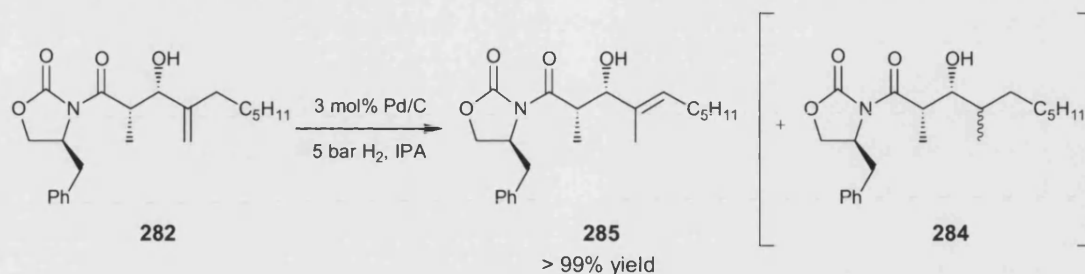
Since the tri-substituted alkene functionality of unsaturated aldol **285** was not hydrogenated during the reaction it was decided to determine whether hydrogen gas was taking part in the reaction. Aldol **282** was treated with 3 mol% palladium on carbon in IPA at atmospheric pressure in the absence of hydrogen gas to see if the isomerisation reaction would still occur (see Scheme 185). After 3 hours, ^1H NMR spectroscopic analysis showed only starting material present in the reaction mixture. The reaction was left for a further 24 hours, however once again only starting material could be observed in the ^1H NMR spectrum, indicating that the presence of hydrogen gas was playing a key role in the rearrangement mechanism of this reaction.



Scheme 185. Palladium on carbon reaction of **282** in the absence of hydrogen gas

Surprisingly, it was found that increasing the hydrogen pressure to 5 bar still resulted in the isomerisation reaction occurring very cleanly, with less than 1% yield of the expected reduced aldol **284** present in the ^1H NMR spectrum of the crude product (see Scheme 186). This was a remarkable observation since it was thought that higher hydrogen pressure

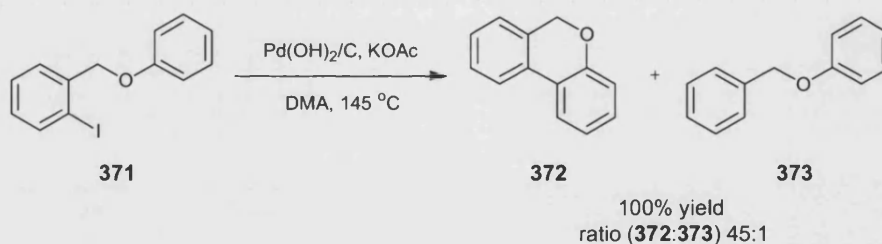
would result in the hydrogenation reaction dominating over the isomerisation reaction, however this does not appear to be the case.



Scheme 186. Palladium on carbon isomerisation of aldol **282** at increased hydrogen pressure

5.3 Effect of palladium source on the reaction

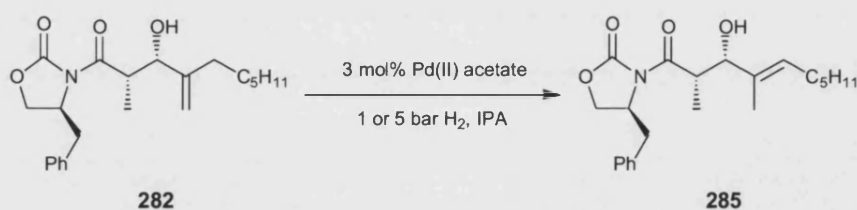
Recently there have been several reports of soluble palladium nanoparticles acting as homogeneous catalysts in a variety of reactions, which had proposed that palladium could ‘leach’ into solution to form soluble palladium species which are responsible for catalytic reaction.^{[222],[223,224]} For example, soluble palladium species arising from insoluble palladium on carbon had been reported to catalyse intra- and inter-molecular ligand-free direct arylation reactions of species such as **371** in polar solvents (see Scheme 187).^[225]



Scheme 187. Ligand free intramolecular arylation using soluble palladium species arising from $\text{Pd(OH)}_2/\text{C}$

Consequently it was considered that the isomerisation reaction of *syn*-aldol **282** might have arisen from the catalytic activity of a soluble palladium species.

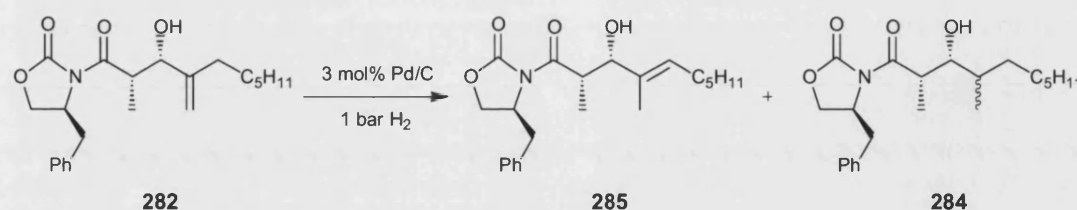
In order to investigate this hypothesis, the isomerisation reaction was repeated using 3 mol% of palladium (II) acetate as a soluble palladium source, under otherwise identical conditions (see Scheme 188). At both 1 bar and 5 bar hydrogen pressure the reaction with palladium (II) acetate occurred cleanly to give isomerised product **285**, with only trace amounts of reduced aldol **284** being observed in the ^1H NMR spectrum of the crude product. This indicated that soluble palladium could indeed be involved in the isomerisation reaction of unsaturated aldol **282**, and therefore that the choice of solvent used in this reaction may also be important.



Scheme 188. Isomerisation of aldol **282** with palladium acetate

5.4 Effect of solvent on the reaction

In order to see what effect the choice of solvent had on the isomerisation reaction, unsaturated aldol product **282** was treated with 3 mol% palladium on carbon at 1 bar pressure using a range of different solvents. After 3 hours the ^1H NMR spectrum of the crude product was analysed and the results are summarised in Table 5.1.



Solvent	Ratio 282 : 285 : 284
isopropyl alcohol	0 : 99 : 1
ethanol	0 : 97 : 3
ether	1 : 97 : 2
dichloromethane	0 : 98 : 2
toluene	1 : 95 : 4
hexane	61 : 38 : 1

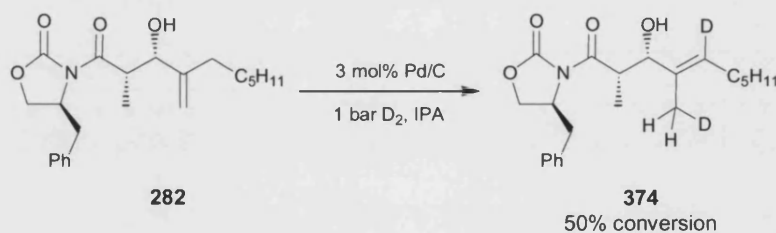
Table 5.1 Effect of solvent on palladium on carbon isomerisation of aldol **282**

Serendipitously, the isomerisation proceeded best in IPA which was the original solvent employed in the reaction. However, it appeared that the reaction was also successful (> 95% isomerised product) in other polar solvents, with only small amounts of starting material **282** or reduced aldol **284** being present. Interestingly the reaction also appeared to be successful using toluene, a non-polar solvent, and even with hexane, although in this case a large amount of starting material remained. These results suggested that the solvent was probably not intrinsically involved in the mechanism of this rearrangement as it had occurred successfully in polar-protic, polar-aprotic and non-polar solvents. It is unclear whether these results support the idea that a soluble palladium species is acting as a catalyst in these reactions, since the literature reports suggest that palladium leaching occurs only in polar solvents such as DME, and is greatly reduced in non-polar solvents such as toluene.^[225]

5.5 Deuterium labelling experiments

In order to further probe the mechanistic aspects of the isomerisation reaction, a series of deuterium labelling experiments were carried out with the aim of determining where the deuterium would be incorporated into the isomerised aldol product **285**.

Unsaturated aldol **282** was initially subjected to isomerisation with 3 mol% palladium on carbon under a balloon of deuterium gas. After 3 hours, the crude ^1H NMR spectrum showed very little conversion ($< 10\%$) to the isomerised product, which was ascribed to a large kinetic isotope effect for deuterium being incorporated into the compound. This was confirmed since after 16 hours only 50% conversion of aldol **282** to the isomerised aldol was observed. This compares to the analogous reaction using hydrogen gas which proceeded to 100% conversion after 3 hours. Analysis of the ^1H NMR spectrum showed that the resonance corresponding to the alkene proton of the isomerised aldol **374** (δ 5.50 ppm) was very small, whilst integration of the resonance corresponding to its new methyl signal (δ 1.57 ppm) was also reduced to two protons. This would indicate that deuterium had been incorporated into both these positions and therefore were not being observed in the ^1H NMR spectrum (see Scheme 189). ^2H NMR spectroscopy confirmed that deuterium had been added into these two sites of the isomerised aldol **374** with deuterium resonances at δ 1.57 ppm and δ 5.50 ppm (see Figure 13).



Scheme 189. Isomerisation carried out under deuterium gas showing incorporation of deuterium into isomerised product **374**

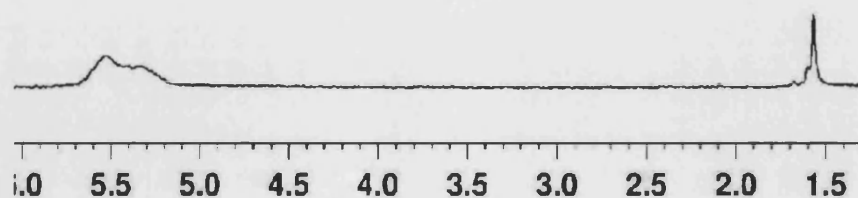
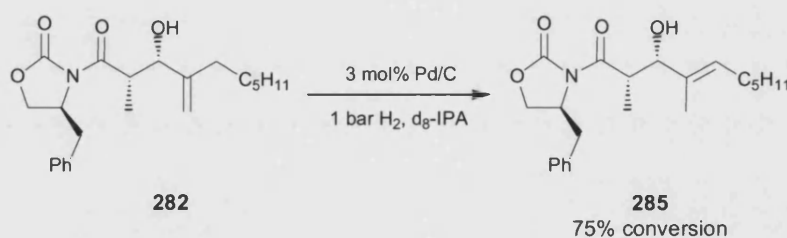


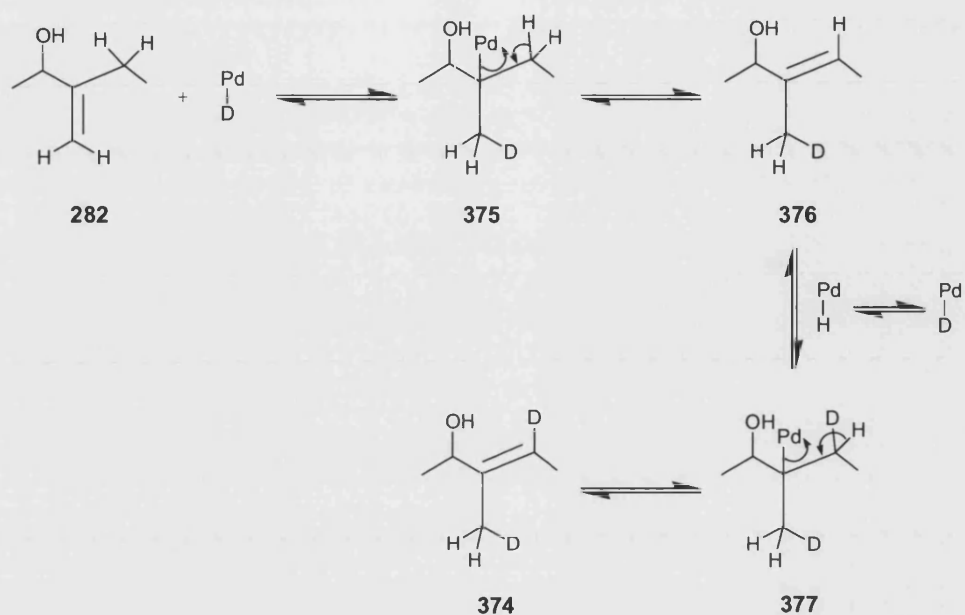
Figure 13. Deuterium NMR spectrum of isomerised aldol **374**

The reaction was then carried out using deuterated d_8 -IPA under 1 bar hydrogen to see if deuterium would be incorporated into the product from the solvent (see Scheme 190). After 3 hours the ^1H NMR spectrum of the crude product showed approximately 50% conversion of starting material **282** and after 16 hours there was 75% conversion to the isomerised product **285**. ^2H NMR analysis of this isomerised aldol **285** showed no significant incorporation of deuterium into the compound, reinforcing the conclusion from the solvent screen that solvent does not play a mechanistic role in this reaction.



Scheme 190. Isomerisation reaction carried out in deuterated solvent

From these results a tentative mechanism was proposed to explain this isomerisation reaction involving addition of a palladium-deuteride catalytic species across the alkene functionality of aldol **282** to afford palladium-deuteride species **375**. This species could then reversibly eliminate Pd-H to afford a new tri-substituted alkene species **376**. Reversible addition of the Pd-D species to alkene **376** would then afford palladium-deuteride species **377** which could further eliminate Pd-H to afford the more stable 1,2-substituted alkene **374** containing two deuterium atoms (see Scheme 191).

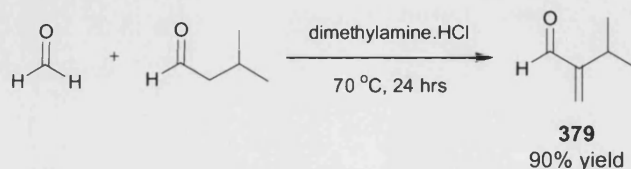


Scheme 191. Proposed mechanism for the palladium-deuteride isomerisation

5.6 Other substrates

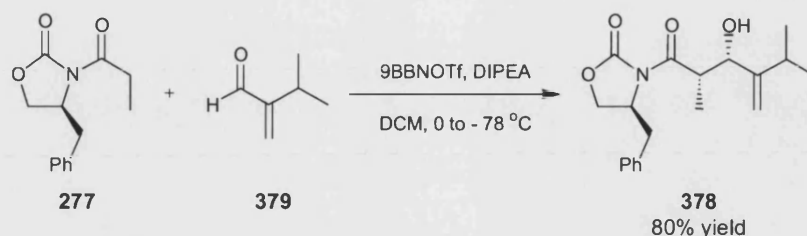
In order to determine whether this palladium promoted isomerisation reaction had the potential to be a useful, generally applicable protocol it was decided to investigate whether it could be applied to other substrates. The tetra-substituted olefin functionality of aldol **378** was therefore chosen as a challenging substrate for this methodology because of its increased steric hindrance.

Consequently, α -methylene aldehyde **379** was first synthesised in good yield from commercially available isovaleraldehyde and formaldehyde, according to the standard procedure described by Marvel *et al.* (see Scheme 192).^[191]



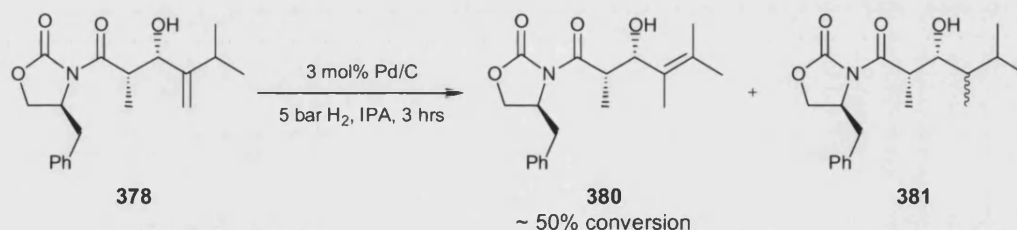
Scheme 192. Synthesis of α -methylene aldehyde **379**

Aldehyde **379** was then employed in a *syn*-aldol reaction with *N*-propionyl-oxazolidin-2-one **277** according to our established procedure to afford unsaturated aldol **378** in 80% yield (see Scheme 193).



Scheme 193. Synthesis of unsaturated aldol **378**

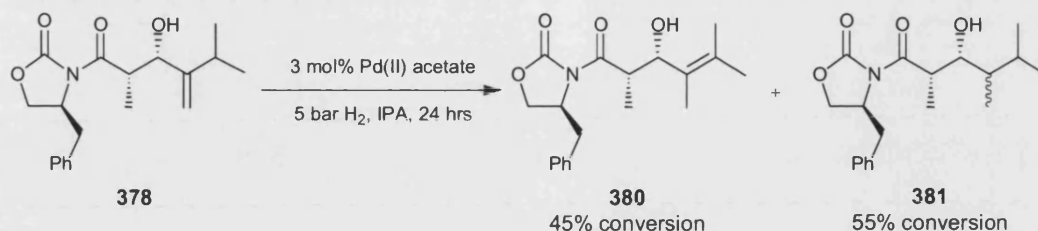
Syn-aldol **378** was then treated with 3 mol% palladium on carbon with 1 bar hydrogen gas under the same conditions described previously. After 3 hours analysis of the ^1H NMR spectrum of the crude product showed very little conversion to the isomerised aldol **380**, which was proposed to be due to increased steric hindrance at the β -position of the alkene fragment. Increasing the hydrogen pressure to 5 bar resulted in approximately 50% conversion to the desired isomerisation product after 3 hours, however the crude ^1H NMR spectrum showed evidence of more than one product, possibly due to formation of the reduced product **381** (see Scheme 194).



Scheme 194. Palladium on carbon isomerisation of aldol **378**

Repeating this reaction using 3 mol% palladium (II) acetate resulted in a much cleaner reaction affording a mixture of starting aldol **378** and isomerised aldol **380** in the ^1H NMR spectrum. However, on leaving the reaction for 24 hours the ^1H NMR spectrum of the crude product showed a mixture of isomerised aldol **380** and reduced product **381** in a

45:55 ratio (see Scheme 195). Fortunately these products could be easily separated by column chromatography to afford an acceptable yield of isomerised aldol **380**.



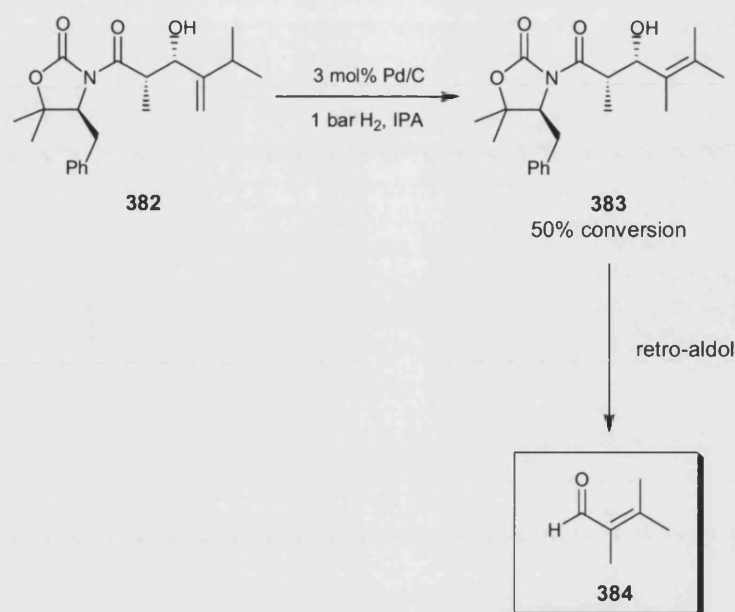
Scheme 195. Palladium (II) acetate isomerisation of aldol **378**

These results suggest that with this substrate there may be an equilibrium between the starting aldol **378** and the isomerised aldol **380** and over time hydrogenation of either substrate may occur. This supports our proposed mechanism that palladium hydride species can add reversibly to the alkene in equilibrium, favouring the most stable isomer.

Therefore, these results show that this isomerisation methodology may be applied to more hindered substrates and further investigation into using this protocol to rearrange different types of α -methylene alcohols is currently being carried out by other members of the SDB group.

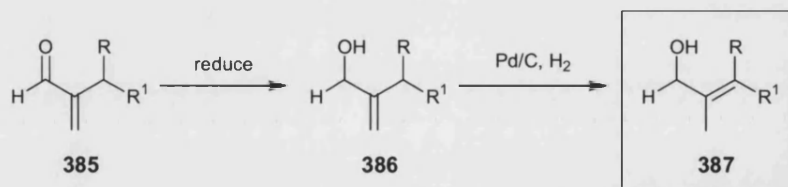
5.7 Future work

It is likely that these isomerised aldol products may undergo retro-aldol reaction which would provide a useful method for the synthesis of highly substituted α,β -unsaturated aldehydes **384** that are difficult to prepare using existing methodology (see Scheme 196).



Scheme 196. Possible synthesis of highly substituted aldehydes

More importantly, the SDB group is currently investigating the scope and limitation of this methodology for the isomerisation of simple methylene alcohols such as **386** into their more substituted analogue **387** (see Scheme 197).



Scheme 197. Possible synthesis of 1,2-substituted allylic alcohols

Chapter 6: Experimental

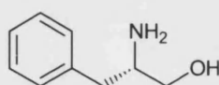
6.1 General conditions

Anhydrous solvents were obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. All commercial reagents were used without purification unless stated otherwise. Hydrogenation catalysts were obtained from Strem Chemicals and were stored and handled under nitrogen, except palladium on carbon which was obtained from Johnson Matthey (10% Pd/charcoal Type 87L). All glassware was dried in an oven and allowed to cool under nitrogen prior to use and all reactions were carried out under nitrogen unless otherwise stated. Hydrogenation reactions were carried out on either the Argonaut Technologies (now Biotage AB) Endeavour[®] catalyst screening system or in a Parr 4714 screwcap pressure vessel. Flash chromatography was performed under medium pressure using matrix 60 silica or Merck Kiesgul 60 unless otherwise stated. Reactions were monitored by TLC on Whatman aluminium baked UV₂₅₄ silica gel plates and visualised under UV. Optical rotations were measured with an AA-10 automatic polarimeter from Optical Rotations Ltd. Proton and carbon magnetic resonance spectra (¹H and ¹³C NMR) were recorded on a Bruker 300MHz spectrometer, using the residual CHCl₃ solvent as an internal standard. The assignment of ¹³C was assisted by DEPT experiments. All chemical shifts (δ) are reported in ppm and J values are recorded in Hz. IR spectra were recorded on a Perkin-Elmer 1605 spectrometer as thin films using NaCl windows or as pressed KBr discs and wavenumbers are reported in cm⁻¹. Mass spectrometry measurements were performed at the EPSRC National Spectrometry Service Centre, University of Wales, Swansea. All compounds were modelled in Spartan 04, *ab initio* calculations were conducted post-conformational search using Hartree-Fock 3-21G(*) level of theory. Compounds were optimised *in vacuo* before application of solvation method PM3HD (assuming hexadecane systems).

6.2 Synthetic procedures and analytical data

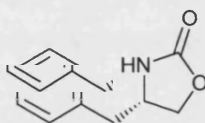
6.2.1 Procedures for the synthesis of (*S*)-4-Benzyl-oxazolidin-2-one (Evans' auxiliary) 276

(*S*)-2-Amino-3-phenyl-propan-1-ol, 275



(*L*)-Phenylalanine (10 g, 0.0605 moles) in dry THF (60mL) was placed in a dry 3 neck flask fitted with double walled condenser, nitrogen bubbler and thermometer under nitrogen. $\text{BF}_3 \cdot \text{OEt}_2$ (1 eq.) was added dropwise over 20 min and the reaction left stirring at room temperature for a further 15 min. The mixture was then heated to reflux in an oil bath and left stirring for 2 hr (solution turns colourless). $\text{BH}_3 \cdot \text{SMe}_2$ (1.25 eq.) was added carefully over 2 hr whilst vigorously refluxing and the reaction left to reflux overnight. The reaction was allowed to cool to room temperature and the excess BH_3 quenched by careful addition of 1:1 THF:water (8mL) followed by 5M NaOH (45mL). The mixture was heated to reflux and left stirring overnight before removing from the oil bath and cooling to room temperature. The white precipitate was filtered off under vacuum and washed with THF. The collected filtrate was evaporated *in vacuo* to remove most of the THF. The organics were extracted into DCM, washed with brine and dried (MgSO_4) before evaporating *in vacuo*. The crude product was recrystallised in hot ethyl acetate to yield (*S*)-2-amino-3-phenyl-propan-1-ol **275** (8.40 g, 92%) as a white crystalline solid, with spectroscopic data essentially identical to the literature compound.^[175]

mp 89 °C [lit. 89.5 – 91.5 °C]; $[\alpha]_D^{25}$ - 23.4 ° (c 1.03, ethanol) [lit. - 24.7 ° (c 1.03, ethanol)]; ^1H NMR (CDCl_3 , 300 MHz): δ 1.63 (3H, broad peak, NH_2 , OH), 2.46 (1H, dd, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$, $J = 13.6, 8.7$ Hz), 2.71 (1H, dd, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$, $J = 13.6, 5.3$ Hz), 3.04 (1H, m, CHNH_2), 3.35 (1H, dd, $\text{CH}_\text{A}\text{H}_\text{B}\text{OH}$, $J = 10.3, 7.2$ Hz), 3.58 (1H, dd, $\text{CH}_\text{A}\text{H}_\text{B}$, $J = 10.3, 3.8$ Hz), 7.19 (5H, m, Ph); ^{13}C NMR (CDCl_3 , 75 MHz): δ 41.8 (CH_2Ph), 54.7 (CHNH_2), 66.8 (CH_2OH), 126.8 (phenyl CH), 128.9 (phenyl CH), 129.6 (phenyl CH), 140.00 (phenyl C); IR (KBr disc) ν_{max} (cm^{-1}): 3625 (N-H), 3364 (broad O-H)

(S)-4-Benzyl-oxazolidin-2-one, 276

2-Amino-3-phenyl-propan-1-ol **275** (3 g, 0.020 moles) was placed in a 2 neck flask fitted with distillation apparatus (distillation head clad with cotton wool and foil). Potassium carbonate (0.1 eq.) and diethyl carbonate (2.06 eq.) are added and the mixture lowered into an oil bath pre heated to 135°C. The distillation receiver was cooled in an ice bath and approximately 2.6 mL of ethanol was collected over 4 hours. The yellow mixture was allowed to cool to room temperature and diluted with DCM, washed with water, dried (MgSO₄), filtered and evaporated *in vacuo*. The crude material was recrystallised in hot 2:1 ethyl acetate:cyclohexane to yield **(S)-4-benzyl-oxazolidin-2-one 276** (2.01 g, 57%) as an off white solid with spectroscopic data essentially identical to literature compound.^[175]

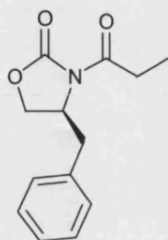
mp 82 °C [lit. 87 °C]; $[\alpha]_D^{25} + 4.8^\circ$ (c 1.10, ethanol) [lit. + 4.9 ° (c 1.10, ethanol)]; ¹H NMR (CDCl₃, 300 MHz): δ 2.80 (2H, m, CH₂Ph), 4.11 (2H, m, CH₂O), 4.40 (1H, app t, CHNH, J = 8.6 Hz), 5.08 (1H, broad s, NH), 7.09-7.39 (5H, broad m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 42.00 (CH₂Ph), 54.3 (CHNH), 70.1 (CH₂O), 127.7 (phenyl CH), 129.4 (phenyl CH), 129.5 (phenyl CH), 136.4 (phenyl C), 159.4 (C=O); IR (KBr disc) ν_{\max} (cm⁻¹): 3460 (N-H), 1760 (C=O)

6.2.2 Typical procedure for the *N*-acylation of **(S)-4-Benzyl-oxazolidin-2-one (Evans' auxiliary) 276**

(S)-4-Benzyl-oxazolidin-2-one 276 (1 eq.) in dry THF was cooled to – 78 °C before addition of butyl lithium (1.01 eq., 2.5 M solution in hexanes) slowly over a 10 minute period followed by the acid chloride (1.1 eq.). The mixture was left stirring at - 78 °C for 45 minutes before warming to room temperature whilst stirring for 1 hour and excess acid chloride quenched by addition of aqueous ammonium chloride. Most of the THF and hexane was removed by evaporation *in vacuo* and the organics extracted with DCM. The combined organic extracts were washed with 1 M NaOH and brine, dried (MgSO₄),

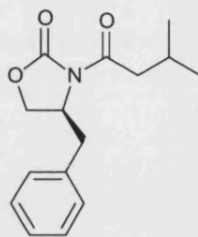
filtered and evaporated *in vacuo*. The resulting oil was left in the fridge overnight to form a crystalline solid. The crude material was recrystallised in hot cyclohexane.

(S)-4-Benzyl-3-propionyl-oxazolidin-2-one, 277



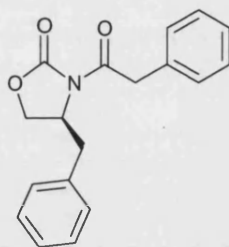
According to general procedure 6.2.2, employing 4-benzyl-oxazolidin-2-one **276** (0.60 g, 3.39 mmol) in THF (10 mL), butyl lithium (1.37 mL, 2.5 M, 3.42 mmol), propionyl chloride (0.33 mL, 3.73 mmol), the crude product was prepared as a colourless oil. Recrystallisation in hot cyclohexane afforded **(S)-4-benzyl-3-propionyl-oxazolidin-2-one 277** (0.74 g, 94%) as an almost colourless crystalline solid, with spectroscopic data essentially identical to literature compound.^[226]

mp 43 °C [lit. 41.2 °C]; $[\alpha]_D^{25} + 93.2^\circ$ (c 1.01, ethanol) [lit. + 92.3 ° (c 1.00, ethanol)]; ¹H NMR (CDCl₃, 300 MHz): δ 1.14 (3H, t, CH₃, J = 7.3 Hz), 2.72 (1H, dd, CH_AH_BPh, J = 13.4 Hz, 9.8 Hz), 2.88 (2H, m, CH₂CH₃), 3.23 (1H, dd, CH_AH_BPh, J = 13.4 Hz, 3.4 Hz), 4.11 (2H, m, CH₂O), 4.61 (1H, m, CHN), 7.21 (5H, broad m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 8.8 (CH₃), 29.1 (CH₂CH₃), 38.2 (CH₂Ph), 55.4 (CHN), 66.5 (CH₂O), 127.7 (phenyl CH), 129.3 (phenyl CH), 129.8 (phenyl CH), 135.6 (phenyl C), 154.00 (OC=O), 174.56 (NC=O); IR (KBr disc) ν_{max} (cm⁻¹): 1786 (C=O), 1701 (C=O)

(S)-4-Benzyl-3-(3-methyl-butyryl)-oxazolidin-2-one, 278

According to general procedure 6.2.2, employing 4-benzyl-oxazolidin-2-one **276** (1.00 g, 5.64 mmol) in THF (15 mL), butyl lithium (2.28 mL, 2.5 M, 5.70 mmol), isovaleryl chloride (0.76 mL, 6.20 mmol), the crude product was prepared as a pale yellow oil. Purification via column chromatography afforded **4-benzyl-3-(3-methyl-butyryl)-oxazolidin-2-one 278** (1.25 g, 85%) as a white solid, with spectroscopic data essentially identical to literature compound.^[227]

mp 50 – 51 °C [lit. 50 – 51 °C]; $[\alpha]_D^{25} + 61.5^\circ$ (c 1.04, CHCl₃) [lit. + 55.8 ° (c 1.01, CHCl₃)]; ¹H NMR (CDCl₃, 300 MHz): δ 0.94 (3H, d, CH₃, J = 6.8 Hz), 0.95 (3H, d, CH₃, J = 6.8 Hz), 2.15 (1H, apparent septet, CH(CH₃)₂, J = 6.8), 2.68 (1H, dd, CH_AH_BPh, J = 13.2, 9.3 Hz), 2.70 (1H, dd, CH_AH_BCH(CH₃)₂, J = 16.2, 7.2 Hz), 2.82 (1H, dd, CH_AH_BCH(CH₃)₂, J = 16.2, 6.8 Hz), 3.24 (1H, dd, CH_AH_BPh, J = 13.2, 3.4 Hz), 4.10 (2H, m, CH₂O), 4.61 (1H, m, CHN), 7.12 – 7.30 (5H, m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 22.8 (CH₃), 23.00 (CH₃), 25.4 (CH(CH₃)₂), 38.4 (CH₂Ph), 44.4 (C=OCH₂), 55.6 (CHN), 66.5 (CH₂O), 127.7 (phenyl CH), 129.3 (phenyl CH), 129.8 (phenyl CH), 135.8 (phenyl C), 153.5 (OC=O), 173.1 (NC=O); IR (KBr disc) ν_{\max} (cm⁻¹): 1787 (C=O), 1694 (C=O)

(S)-4-Benzyl-3-phenylacetyl-oxazolidin-2-one, 279

According to general procedure 6.2.2, employing 4-benzyl-oxazolidin-2-one **276** (1.00 g, 5.64 mmol) in THF (15 mL), butyl lithium (2.28 mL, 2.5 M, 5.70 mmol), phenyl acetyl chloride (0.82 mL, 6.20 mmol), the crude product was prepared as a yellow oil. Purification by column chromatography afforded **(S)-4-benzyl-3-phenylacetyl-oxazolidin-2-one 279** (1.45 g, 87%) as a white solid, with spectroscopic data essentially identical to literature compound.^[227]

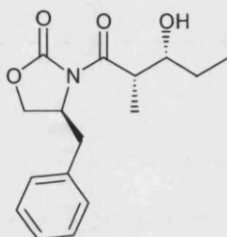
mp 69 °C [lit. 71.5 °C]; $[\alpha]_D^{25} + 75.7^\circ$ (c 1.01, CHCl₃) [lit. + 72.4 ° (c 1.01, CHCl₃)]; ¹H NMR (CDCl₃, 300 MHz): δ 2.69 (1H, dd, CH_AH_BPh, J = 13.4 Hz, 9.4 Hz), 3.20 (1H, dd, CH_AH_BPh, J = 13.4 Hz, 3.3 Hz), 4.11 (2H, m, CH₂O), 4.20 (1H, d, C(O)CH_AH_BPh, J = 15.4 Hz), 4.27 (1H, d, C(O)CH_AH_BPh, J = 15.4 Hz), 4.60 (1H, m, CHN), 7.06 (2H, dd, Ph, J = 7.5 Hz, 1.9 Hz), 7.17-7.30 (8H, broad m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 37.6 (CHCH₂Ph), 41.4 (C=OCH₂Ph), 55.2 (CHN), 66.0 (CH₂O), 127.1 (phenyl CH), 128.4 (phenyl CH), 128.8 (phenyl CH), 129.3 (phenyl CH), 129.7 (phenyl CH), 133.4 (phenyl C), 135.0 (phenyl C), 153.3 (OC=O), 171.1 (NC=O); IR (KBr disc) ν_{\max} (cm⁻¹): 1776 (C=O), 1698 (C=O)

6.2.3 Typical procedure for the Evans auxiliary mediated *syn*-aldol reaction

A solution of *N*-acylated oxazolidinone (1 eq.) in DCM was cooled to 0 °C in an ice bath and 9-BBNOTf (1.1 eq., 0.5 M solution in hexanes) added dropwise. The mixture was left stirring for 30 min at 0 °C before addition of diisopropylethylamine (1.3 eq.) and stirring for a further 40 min. The reaction was then cooled to – 78 °C in an acetone-dry ice bath before addition of the aldehyde (1.1 eq.) and stirring for 1 hr at – 78 °C followed by 1 hr at 0 °C. The mixture was allowed to warm to room temperature, pH 7 phosphate buffer added and stirred for 5 min before addition of 2:1 hydrogen peroxide:methanol (v/v) and stirring

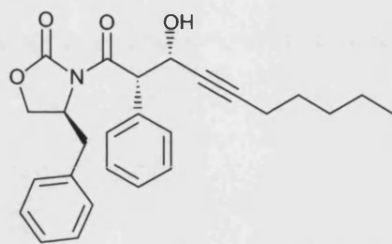
for 16 hrs. The bulk of the solvent was removed *in vacuo* and the resulting slurry partitioned between water and diethyl ether. The combined organic extracts were washed with 5 % Na₂CO₃ and brine, dried (MgSO₄), filtered and evaporated *in vacuo*.

(S)-4-Benzyl-3-((2S,3R)-3-hydroxy-2-methyl-pentanoyl)-oxazolidin-2-one, 280



According to general procedure 6.2.3, employing (S)-4-benzyl-3-propionyl-oxazolidin-2-one **277** (0.35 g, 1.50 mmol) in DCM (15 mL), 9-BBNOTf (3.60 mL, 1.80 mmol), diisopropylethylamine (0.34 mL, 1.95 mmol), propionaldehyde (0.12 mL, 1.65 mmol), the crude product was prepared as a pale yellow oil. Purification by column chromatography afforded (S)-4-benzyl-3-((2S,3R)-3-hydroxy-2-methyl-pentanoyl)-oxazolidin-2-one **280** (0.4 g, 91%) as an off white solid, with spectroscopic data essentially identical to the literature compound.^[228]

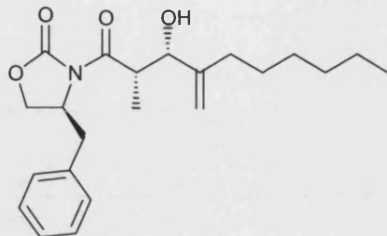
mp 78 °C [lit. 77 – 79 °C]; $[\alpha]_D^{25} - 94.0^\circ$ (c 1.06, ethanol) [+ 38.5 ° (c 1.07, CHCl₃)]; ¹H NMR (CDCl₃, 300 MHz): δ 0.91 (3H, t, CH₂CH₃, J = 7.4 Hz), 1.20 (3H, d, CHCH₃, J = 7.2 Hz), 1.36 – 1.57 (2H, m, CH₂CH₃), 2.74 (1H, dd, CH_AH_BPh, J = 13.6, 9.6 Hz), 2.87 (1H, broad singlet, OH), 3.19 (1H, dd, CH_AH_BPh, J = 13.6, 3.4 Hz), 3.73 (1H, qd, CHCH₃, J = 7.2, 2.6 Hz), 3.80 (1H, m, CHOH), 4.14 (2H, m, CH₂O), 4.64 (1H, m, CHN), 7.11-7.31 (5H, broad m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 10.7 (CH₃), 10.8 (CH₃), 38.2 (CH₂Ph), 42.1 (CHCH₃), 55.5 (CHN), 66.6 (CH₂O), 73.4 (CHOH), 128.0 (phenyl CH), 129.4 (phenyl CH), 129.8 (phenyl CH), 135.1 (phenyl C), 153.5 (OC=O), 177.8 (NC=O); IR (KBr disc) ν_{max} (cm⁻¹): 3510 (O-H), 1777 (C=O), 1689 (C=O); HRMS: m/z (ES) [M+H]⁺ requires 292.1543, found 292.1546

(*S*)-4-Benzyl-3-((2*S*,3*S*)-3-hydroxy-2-phenyl-dec-4-ynoyl)-oxazolidin-2-one, 281

According to general procedure 6.2.3, employing (*S*)-4-benzyl-3-phenylacetyl-oxazolidin-2-one **279** (0.30 g, 1.02 mmol) in DCM (15 mL), 9-BBNOTf (2.44 mL, 0.5 M, 1.22 mmol), diisopropylethylamine (0.23 mL, 1.33 mmol) and oct-2-ynal (0.14 g, 1.12 mmol), the crude product was prepared as a yellow oil. Purification by column chromatography afforded (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-phenyl-dec-4-ynoyl)-oxazolidin-2-one **281** (0.34 g, 80%) as a pale yellow oil.

$[\alpha]_D^{25}$ - 36.5 ° (c 1.0, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 0.82 (3H, t, CH₃, J = 7.2 Hz), 1.24 (4H, m, C₂H₄), 1.41 (2H, m, CH₂), 2.12 (2H, dt, C≡CCH₂, J = 7.2 Hz, 1.9 Hz), 2.27 (1H, d, OH, J = 4.5 Hz), 2.55 (1H, dd, CH_AH_BPh, J = 13.6 Hz, 9.0 Hz), 3.07 (1H, dd, CH_AH_BPh, J = 13.6 Hz, 3.4 Hz), 4.04 (1H, dd, CH_AH_BO, J = 9.0 Hz, 3.0 Hz), 4.13 (1H, app t, CH_AH_BO, J = 9.0 Hz), 4.70 (1H, m, CHN), 4.96 (1H, m, CHOH), 5.18 (1H, d, CHPh, J = 7.2 Hz), 6.93 (2H, m, Ph), 7.19 (4H, broad m, Ph), 7.31 (4H, broad m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 14.4 (CH₃), 19.1 (CH₂), 22.6 (CH₂), 28.7 (CH₂), 31.4 (CH₂), 37.7 (CH₂Ph), 55.2 (CHN), 56.2 (CHPh), 64.1 (CHOH), 66.3 (CH₂O), 79.2 (C≡C), 87.7 (C≡C), 127.7 (phenyl CH), 128.6 (phenyl CH), 129.1 (phenyl CH), 129.3 (phenyl CH), 130.3 (phenyl CH), 131.0 (phenyl CH), 133.9 (phenyl C), 135.1 (phenyl C), 153.0 (OC=O), 178.3 (NC=O); IR (thin film) ν_{max} (cm⁻¹): 3520 (O-H), 1765 (C=O), 1700 (C=O); HRMS: m/z (ES) [M+H]⁺ requires 420.2171, found 420.2173

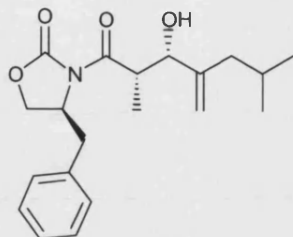
(*S*)-4-Benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylene-decanoyl)-oxazolidin-2-one, 282



According to general procedure 6.2.3, employing (*S*)-4-benzyl-3-propionyl-oxazolidin-2-one **277** (1.5 g, 6.4 mmol) in DCM (65 mL), 9-BBNOTf (14.15 mL, 0.5 M, 7.04 mmol), diisopropylethylamine (1.46 mL, 8.32 mmol), 2-methylene-octanal **283** (0.99 g, 7.04 mmol), the crude product was prepared as a pale yellow oil. Purification by column chromatography afforded (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylene-decanoyl)-oxazolidin-2-one **282** (2.39 g, 85%) as a colourless oil.

$[\alpha]_D^{25} + 38.0^\circ$ (c 1.0, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz): δ 0.86 - 0.89 (3H, broad m, CH_2CH_3), 1.18 (8H, m, C_4H_8), 1.25 - 1.32 (3H, broad m, CHCH_3), 1.99 (2H, m, $\text{CH}_2\text{C}=\text{CH}_2$), 2.73 (1H, dd, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$, $J = 13.5$ Hz, 8.9 Hz), 2.97 (1H, broad s, OH), 3.21 (1H, dd, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$, $J = 13.5$ Hz, 3.5 Hz), 3.96 (1H, m, CHCH_3), 4.21 (2H, m, CH_2O), 4.44 (1H, m, CHOH), 4.63 (1H, m, CHN), 4.93 (1H, m, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 5.12 (1H, m, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 7.10 - 7.31 (5H, broad m, Ph); ^{13}C NMR (CDCl_3 , 75 MHz): δ 10.1 (CH_3), 14.0 (CH_3), 22.6 (CH_2), 27.9 (CH_2), 29.1 (CH_2), 31.7 (CH_2), 32.7 (CH_2), 37.7 (CH_2Ph), 40.3 (CHCH_3), 55.2 (CHN), 66.2 (CH_2O), 73.1 (CHOH), 110.4 ($\text{C}=\text{CH}_2$), 127.4 (phenyl CH), 128.9 (phenyl CH), 129.4 (phenyl CH), 135.0 (phenyl C), 148.2 ($\text{C}=\text{CH}_2$), 152.9 ($\text{OC}=\text{O}$), 177.2 ($\text{NC}=\text{O}$); IR (thin film) ν_{max} (cm^{-1}): 3521 (O-H), 3029 (C=C), 1780 (C=O), 1700 (C=O); HRMS: m/z (ES) $[\text{M}+\text{H}]^+$ requires 374.2326, found 374.2329

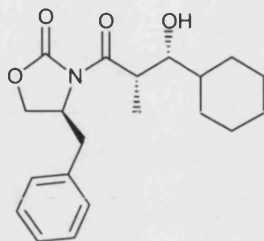
(*S*)-4-Benzyl-3-((2*S*,3*S*)-3-hydroxy-2,6-dimethyl-4-methylene-heptanoyl)-oxazolidin-2-one, 292



According to general procedure 6.2.3, employing (*S*)-4-benzyl-3-propionyl-oxazolidin-2-one **277** (0.50 g, 2.14 mmol) in DCM (25 mL), 9-BBNOTf (4.72 mL, 0.5 M, 2.35 mmol), diisopropylethylamine (0.49 mL, 2.78 mmol), 4-methyl-2-methylene-pentanal **293** (0.26 g, 2.35 mmol), the crude product was prepared as a pale yellow oil. Purification by column chromatography afforded (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2,6-dimethyl-4-methylene-heptanoyl)-oxazolidin-2-one **292** (0.58 g, 79%) as a pale yellow oil.

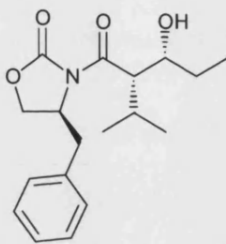
$[\alpha]_D^{25} + 26.7^\circ$ (c 1.31, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz): δ 0.88 (3H, d, $\text{CH}(\text{CH}_3)_2$, $J = 6.4\text{ Hz}$), 0.91 (3H, d, $\text{CH}(\text{CH}_3)_2$, $J = 6.4\text{ Hz}$), 1.19 (3H, d, CHCH_3 , $J = 6.8\text{ Hz}$), 1.80 (1H, m, $\text{CH}(\text{CH}_3)_2$), 1.88 (2H, d, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $J = 6.0\text{ Hz}$), 2.80 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, $J = 13.6, 9.4\text{ Hz}$), 2.99 (1H, d, OH, $J = 3.0\text{ Hz}$), 3.26 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, $J = 13.6, 3.4\text{ Hz}$), 3.94 (1H, qd, CHCH_3 , $J = 7.2, 3.0\text{ Hz}$), 4.22 (2H, m, CH_2O), 4.42 (1H, apparent s, CHOH), 4.71 (1H, m, CHN), 4.98 (1H, t, $\text{C}=\text{CH}_A\text{H}_B$, $J = 1.3\text{ Hz}$), 5.24 (1H, t, $\text{C}=\text{CH}_A\text{H}_B$, $J = 1.7\text{ Hz}$), 7.19 – 7.37 (5H, m, Ph); ^{13}C NMR (CDCl_3 , 75 MHz): δ 10.0 (CH_3), 22.1 ($\text{CH}(\text{CH}_3)_2$), 22.8 ($\text{CH}(\text{CH}_3)_2$), 26.4 ($\text{CH}(\text{CH}_3)_2$), 37.7 (CH_2Ph), 40.0 (CHCH_3), 42.6 (CH_2), 55.2 (CHN), 66.2 (CH_2O), 72.7 (CHOH), 111.9 ($\text{C}=\text{CH}_2$), 127.4 (phenyl CH), 129.0 (phenyl CH), 129.4 (phenyl CH), 135.0 (phenyl C), 146.5 ($\text{C}=\text{CH}_2$), 152.9 ($\text{OC}=\text{O}$), 177.3 ($\text{NC}=\text{O}$); IR (thin film) ν_{max} (cm^{-1}): 3538 (O-H), 1795 ($\text{C}=\text{O}$), 1685 ($\text{C}=\text{O}$); HRMS: m/z (ES) $[\text{M}+\text{H}]^+$ requires 346.2013, found 346.2015

(*S*)-4-Benzyl-3-((2*S*,3*R*)-3-cyclohexyl-3-hydroxy-2-methyl-propionyl)-oxazolidin-2-one, 306



According to general procedure 6.2.3, employing (*S*)-4-benzyl-3-propionyl-oxazolidin-2-one **277** (0.50 g, 2.14 mmol) in DCM (10 mL), 9-BBNOTf (4.71 mL, 0.5 M, 2.35 mmol), diisopropylethylamine (0.48 mL, 2.78 mmol), cyclohexanecarbaldehyde (0.29 mL, 2.35 mmol), the crude product was prepared as a yellow oil. Purification by column chromatography afforded (*S*)-4-benzyl-3-((2*S*,3*R*)-3-cyclohexyl-3-hydroxy-2-methyl-propionyl)-oxazolidin-2-one **306** (0.74 g, 90%) as a pale yellow oil.

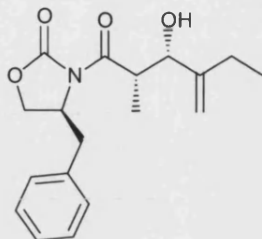
$[\alpha]_D^{25} + 26.4^\circ$ (c 1.21, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz): δ 0.97 (2H, broad m, cyclohexyl CH_2), 1.18 (2H, broad m, cyclohexyl CH_2), 1.23 (3H, d, CH_3 , $J = 7.2$ Hz), 1.40 (2H, broad m, CH_2), 1.66 (2H, broad m, cyclohexyl CH_2), 1.75 (2H, broad m, cyclohexyl CH_2), 2.10 (1H, broad m, cyclohexyl CH), 2.78 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, $J = 13.6, 9.4$ Hz), 3.26 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, $J = 13.6, 3.4$ Hz), 3.60 (1H, dd, CHOH , $J = 8.7, 2.3$ Hz), 3.95 (1H, qd, CHCH_3 , $J = 7.2, 2.3$ Hz), 4.20 (2H, m, CH_2O), 4.70 (1H, m, CHN), 7.18 – 7.37 (5H, broad m, Ph); ^{13}C NMR (CDCl_3 , 75 MHz): δ 9.6 (CH_3), 25.9 (CH_2), 28.6 (CH_2), 29.6 (CH_2), 37.6 (CH_2Ph), 39.1 (CH), 40.0 (CHCH_3), 55.1 (CHN), 66.1 (CH_2O), 75.4 (CHOH), 127.3 (phenyl CH), 128.9 (phenyl CH), 129.3 (phenyl CH), 135.0 (phenyl C), 153.2 (OC=O), 177.8 (NC=O); IR (thin film) ν_{max} (cm^{-1}): 3481 (O-H), 1751 (C=O), 1688 (C=O); HRMS: m/z (ES) $[\text{M}+\text{H}]^+$ requires 346.2013, found 346.2017

(S)-4-Benzyl-3-((2S,3R)-3-hydroxy-2-isopropyl-pentanoyl)-oxazolidin-2-one, 307

According to general procedure 6.2.3, employing (S)-4-benzyl-3-(3-methyl-butyl)-oxazolidin-2-one **278** (1.00 g, 3.83 mmol) in DCM (50 mL), 9-BBNOTf (8.43 mL, 0.5 M, 4.21 mmol), diisopropylethylamine (0.87 mL, 4.98 mmol), propionaldehyde (0.24 g, 4.21 mmol), the crude product was prepared as a pale yellow oil. Purification by column chromatography afforded **(S)-4-benzyl-3-((2S,3R)-3-hydroxy-2-isopropyl-pentanoyl)-oxazolidin-2-one 307** (0.88 g, 72%) as a cloudy oil.

$[\alpha]_D^{25} + 25.0^\circ$ (c 1.00, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz): δ 1.00 (9H, m, CH_3 and $\text{CH}(\text{CH}_3)_2$), 1.47 (1H, m, $\text{CH}_A\text{H}_B\text{CH}_3$), 1.61 (1H, m, $\text{CH}_A\text{H}_B\text{CH}_3$), 2.25 (1H, m, $\text{CH}(\text{CH}_3)_2$), 2.63 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, $J = 13.2, 10.5$ Hz), 3.42 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, $J = 13.2, 3.4$ Hz), 3.93 (1H, m, CHOH), 4.07 (1H, dd, $\text{CH}-i\text{Pr}$, $J = 8.7, 6.0$ Hz), 4.14 (2H, m, CH_2O), 4.75 (1H, m, CHN), 7.22 – 7.37 (5H, m, Ph); ^{13}C NMR (CDCl_3 , 75 MHz): δ 11.1 (CH_3), 20.7 (CH_3), 21.4 (CH_3), 25.8 (CH_2), 28.6 (CH), 38.6 (CH_2Ph), 54.5 (CH), 56.0 (CH), 66.3 (CH_2O), 73.7 (CHOH), 127.7 (phenyl CH), 129.3 (phenyl CH), 129.7 (phenyl CH), 135.8 (phenyl C), 154.3 ($\text{OC}=\text{O}$), 174.9 ($\text{NC}=\text{O}$); IR (thin film) ν_{max} (cm^{-1}): 3521 (O-H), 1772 ($\text{C}=\text{O}$), 1699 ($\text{C}=\text{O}$)

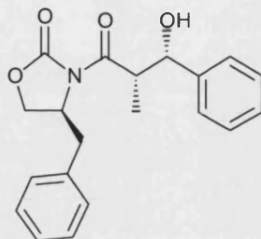
(*S*)-4-Benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylene-hexanoyl)-oxazolidin-2-one, 308



According to general procedure 6.2.3, employing (*S*)-4-benzyl-3-propionyl-oxazolidin-2-one **277** (0.50 g, 2.14 mmol) in DCM (10 mL), 9-BBNOTf (4.71 mL, 0.5 M, 2.35 mmol), diisopropylethylamine (0.48 mL, 2.78 mmol) and 2-ethyl-propenal (0.20 g, 2.35 mmol), the crude product was prepared as a pale yellow oil. Purification by column chromatography afforded (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylene-hexanoyl)-oxazolidin-2-one **308** (0.56 g, 83%) as a colourless viscous oil.

$[\alpha]_D^{25} + 35.0^\circ$ (c 1.00, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 1.12 (3H, t, CH₃, J = 7.5 Hz), 1.23 (3H, d, CHCH₃, J = 7.2 Hz), 2.07 (2H, m, CH₂CH₃), 2.84 (1H, dd, CH_AH_BPh, J = 13.6, 9.4 Hz), 3.00 (1H, broad s, OH), 3.31 (1H, dd, CH_AH_BPh, J = 13.6, 3.4 Hz), 4.00 (1H, qd, CHCH₃, J = 7.2, 3.0 Hz), 4.26 (2H, m, CH₂O), 4.50 (1H, apparent s, CHOH), 4.76 (1H, m, CHN), 5.04 (1H, apparent t, C=CH_AH_B, J = 1.5 Hz), 5.23 (1H, apparent t, C=CH_AH_B, J = 1.1 Hz), 7.23 – 7.42 (5H, m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 10.1 (CH₃), 12.1 (CH₃), 25.3 (CH₂), 37.7 (CH₂Ph), 40.3 (CHCH₃), 55.2 (CHN), 66.2 (CH₂O), 73.2 (CHOH), 109.5 (C=CH₂), 127.4 (phenyl CH), 128.9 (phenyl CH), 129.4 (phenyl CH), 135.0 (phenyl C), 149.6 (C=CH₂), 152.9 (OC=O), 177.1 (NC=O); IR (thin film) ν_{\max} (cm⁻¹): 3489 (O-H), 1750 (C=O), 1690 (C=O); HRMS: m/z (ES) [M+H]⁺ requires 318.1700, found 318.1702

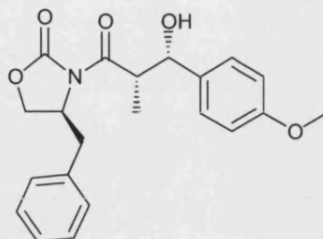
(*S*)-4-Benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-3-phenyl-propionyl)-oxazolidin-2-one, 309



According to general procedure 6.2.3, employing (*S*)-4-benzyl-3-propionyl-oxazolidin-2-one **277** (0.15 g, 0.44 mmol) in DCM (4 mL), 9-BBNOTf (1.06 mL, 0.5 M, 0.53 mmol), diisopropylethylamine (0.10 mL, 0.58 mmol), benzaldehyde (0.049 mL, 0.49 mmol), the crude product was prepared as a dark yellow oil. Purification by column chromatography afforded (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-3-phenyl-propionyl)-oxazolidin-2-one **309** (0.11 g, 75%) as a colourless oil, with spectroscopic data essentially identical to the literature compound.^[229]

$[\alpha]_D^{25} + 54.0^\circ$ (c 1.32, CHCl_3) [lit. + 75.7 (c 1.00, CH_2Cl_2)]; ^1H NMR (CDCl_3 , 300 MHz): δ 1.14 (3H, d, CH_3 , $J = 7.0$ Hz), 2.68 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, $J = 13.5, 9.5$ Hz), 3.10 (1H, broad s, OH), 3.15 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, $J = 13.5, 3.5$ Hz), 4.01 (3H, m, CHCH_3 and CH_2O), 4.49 (1H, m, CHN), 5.00 (1H, d, CHOH , $J = 4.0$ Hz), 7.22 (10H, broad m, Ph); ^{13}C NMR (CDCl_3 , 75 MHz): δ 11.4 (CH_3), 38.10 (CH_2Ph), 45.0 (CHCH_3), 55.6 (CHN), 66.6 (CH_2O), 74.2 (CHOH), 126.5 (phenyl CH), 127.8 (phenyl CH), 127.9 (phenyl CH), 128.6 (phenyl CH), 129.4 (phenyl CH), 129.8 (phenyl CH), 135.4 (phenyl C), 141.7 (phenyl C), 153.3 (OC=O), 177.1 (NC=O); IR (thin film) ν_{max} (cm^{-1}): 3507 (broad O-H), 1770 (C=O), 1698 (C=O); HRMS: m/z (ES) $[\text{M}+\text{H}]^+$ requires 340.1543, found 340.1543

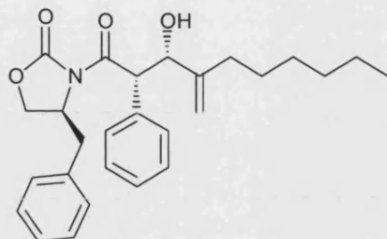
(*S*)-4-Benzyl-3-[(2*S*,3*S*)-3-hydroxy-3-(4-methoxy-phenyl)-2-methyl-propionyl]-oxazolidin-2-one, 310



According to general procedure 6.2.3, employing (*S*)-4-benzyl-3-propionyl-oxazolidin-2-one **277** (0.10 g, 0.43 mmol) in DCM (5 mL), 9-BBNOTf (1.03 mL, 0.5 M, 0.52 mmol), diisopropylethylamine (0.10 mL, 0.56 mmol), 4-methoxy-benzaldehyde (0.06 mL, 0.47 mmol), the crude product was prepared as a pale yellow oil. Purification by column chromatography afforded (*S*)-4-benzyl-3-[(2*S*,3*S*)-3-hydroxy-3-(4-methoxy-phenyl)-2-methyl-propionyl]-oxazolidin-2-one **310** (0.11 g, 68%) as a colourless oil.

$[\alpha]_D^{25} + 41.2^\circ$ (c 1.00, CHCl_3); $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 1.23 (3H, d, CHCH_3 , $J = 6.8$ Hz), 2.76 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, $J = 13.5, 9.4$ Hz), 3.23 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, $J = 13.5, 3.4$ Hz), 3.79 (3H, s, OCH_3), 4.09 (3H, overlapping m, CH_2O , CHCH_3), 4.58 (1H, m, CHN), 5.02 (1H, d, CHOH , $J = 4.5$ Hz), 6.87 (2H, m, Ph), 7.19 – 7.37 (7H, m, Ph); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ 9.8 (CH_3), 38.2 (CH_2Ph), 44.8 (CHCH_3), 55.7 (CHN), 56.1 (OCH_3), 66.8 (CH_2O), 75.0 (CHOH), 114.2 (phenyl CH), 126.6 (phenyl CH), 127.7 (phenyl CH), 128.6 (phenyl CH), 129.8 (phenyl CH), 135.2 (phenyl C), 153.5 (C), 159.3 (C), 177.2 (NC=O); IR (thin film) ν_{max} (cm^{-1}): 3522 (O-H), 1780 (C=O), 1691 (C=O); HRMS: m/z (ES) $[\text{M}+\text{H}]^+$ requires 370.1650, found 370.1652

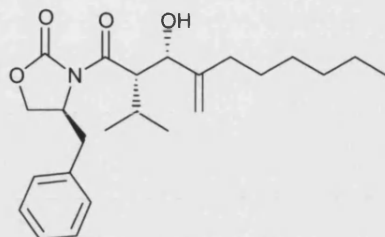
(*S*)-4-Benzyl-3-((2*S*,3*S*)-3-hydroxy-4-methylene-2-phenyl-decanoyl)-oxazolidin-2-one, 311



According to general procedure 6.2.3, employing (*S*)-4-benzyl-3-phenylacetyl-oxazolidin-2-one **279** (1.37 g, 4.64 mmol) in DCM (50 mL), 9-BBNOTf (10.21 mL, 0.5 M, 5.10 mmol), diisopropylethylamine (1.05 mL, 6.03 mmol), 2-methylene-octanal **283** (0.72 g, 5.10 mmol), the crude product was prepared as a pale yellow oil. Purification by column chromatography afforded (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-4-methylene-2-phenyl-decanoyl)-oxazolidin-2-one **311** (1.41 g, 70%) as a pale yellow oil.

$[\alpha]_D^{25}$ - 8.0 ° (c 1.00, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 0.95 - 1.83 (13H, broad m, C₆H₁₃), 2.37 - 2.45 (1H, broad m, OH), 2.77 (1H, dd, CH_AH_BPh, J = 13.2, 9.4 Hz), 3.27 (1H, dd, CH_AH_BPh, J = 13.2, 3.4 Hz), 4.19 (2H, m, CH₂O), 4.23 (1H, d, CHPh, J = 10.2 Hz), 4.32 (1H, d, CHOH, J = 10.2 Hz), 4.69 (1H, m, CHN), 5.99 (1H, d, C=CH_AH_B, J = 0.8 Hz), 6.25 (1H, d, C=CH_AH_B, J = 0.8 Hz), 7.14 (2H, m, Ph), 7.25 - 7.38 (8H, broad m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 14.1 (CH₃), 22.6 (CH₂), 27.8 (CH₂), 29.1 (CH₂), 31.7 (CH₂), 32.4 (CH₂), 37.1 (CH₂Ph), 53.0 (CHPh), 54.7 (CHN), 65.7 (CH₂O), 75.5 (CHOH), 112.0 (C=CH₂), 127.2 (phenyl CH), 128.0 (phenyl CH), 128.6 (phenyl CH), 128.8 (phenyl CH), 129.3 (phenyl CH), 130.0 (phenyl CH), 134.0 (phenyl C), 134.6 (phenyl C), 148.6 (C=CH₂), 152.6 (OC=O), 172.7 (NC=O); IR (thin film) ν_{max} (cm⁻¹): 3516 (O-H), 1771 (C=O), 1700 (C=O); HRMS: m/z (ES) [M+H]⁺ requires 436.2482, found 436.2483

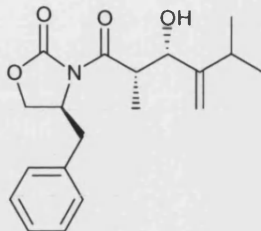
(S)-4-Benzyl-3-((2S,3S)-3-hydroxy-2-isopropyl-4-methylene-decanoyl)-oxazolidin-2-one, 337



According to general procedure 6.2.3, employing (S)-4-benzyl-3-(3-methyl-butyryl)-oxazolidin-2-one **278** (1.19 g, 4.56 mmol) in DCM (50 mL), 9-BBNOTf (10.03 mL, 5.02 mmol), diisopropylethylamine (1.03 mL, 5.93 mmol) and 2-methylene-octanal **283** (0.70 g, 5.02 mmol), the crude product was prepared. Purification by column chromatography afforded **(S)-4-benzyl-3-((2S,3S)-3-hydroxy-2-isopropyl-4-methylene-decanoyl)-oxazolidin-2-one 337** (1.48 g, 81%) as a pale yellow oil.

$[\alpha]_D^{25} + 28.0^\circ$ (c 1.0, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz): δ 0.80 (3H, t, CH_2CH_3 , $J = 6.6$ Hz), 1.03 (6H, d, $\text{CH}(\text{CH}_3)_2$, $J = 6.8$ Hz), 1.14 – 1.42 (8H, m, C_4H_8), 2.00 (2H, m, $\text{CH}_2\text{C}=\text{CH}_2$), 2.20 (1H, d, OH, $J = 4.5$ Hz), 2.30 (1H, m, $\text{CH}(\text{CH}_3)_2$), 2.53 (1H, dd, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$, $J = 13.2, 10.5$ Hz), 3.32 (1H, dd, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$, $J = 13.2, 3.4$ Hz), 4.02 (2H, m, CH_2O), 4.25 (1H, dd, $\text{CH}^\text{i}\text{Pr}$, $J = 7.9, 5.2$ Hz), 4.36 (1H, dd, CHOH , $J = 7.9, 4.5$ Hz), 4.57 (1H, m, CHN), 4.81 (1H, d, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$, $J = 1.5$ Hz), 5.04 (1H, apparent s, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 7.13 – 7.29 (5H, m, Ph); ^{13}C NMR (CDCl_3 , 75 MHz): δ 14.1 (CH_3), 19.9 (CH_3), 20.4 (CH_3), 22.6 (CH_2), 27.8 (CH_2), 29.1 (CH_2), 29.4 (CH), 31.7 (CH_2), 32.3 (CH_2), 37.9 (CH_2Ph), 50.2 ($\text{CH}^\text{i}\text{Pr}$), 55.5 (CHN), 66.3 (CH_2O), 74.3 (CHOH), 111.1 ($\text{C}=\text{CH}_2$), 127.3 (phenyl CH), 129.0 (phenyl CH), 129.3 (phenyl CH), 135.3 (phenyl C), 150.2 ($\text{C}=\text{CH}_2$), 153.3 ($\text{OC}=\text{O}$), 172.7 ($\text{NC}=\text{O}$); IR (thin film) ν_{max} (cm^{-1}): 1782 ($\text{C}=\text{O}$), 1700 ($\text{C}=\text{O}$); HRMS: m/z (ES) $[\text{M}+\text{H}]^+$ requires 402.2639, found 406.2632

(*S*)-4-Benzyl-3-((2*S*,3*S*)-3-hydroxy-2,5-dimethyl-4-methylene-hexanoyl)-oxazolidin-2-one, 378



According to general procedure 6.2.3, employing (*S*)-4-benzyl-3-propionyl-oxazolidin-2-one **277** (2.00 g, 8.57 mmol) in DCM (100 mL), 9-BBNOTf (18.86 mL, 0.5 M, 9.43 mmol), diisopropylethylamine (1.94 mL, 11.14 mmol), 3-methyl-2-methylene-butylaldehyde **379** (0.93 g, 9.43 mmol), the crude product was prepared as a viscous oil. Purification by column chromatography afforded (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2,5-dimethyl-4-methylene-hexanoyl)-oxazolidin-2-one **378** (2.27 g, 80%) as a white solid.

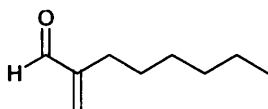
mp 99 – 102 °C; $[\alpha]_D^{25} + 37.1^\circ$ (c 1.16, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 1.06 (3H, d, CH(CH₃)₂, J = 6.8 Hz), 1.09 (3H, d, CH(CH₃)₂, J = 6.8 Hz), 1.20 (3H, d, CHCH₃, J = 6.8 Hz), 2.19 (1H, apparent septet, CH(CH₃)₂, J = 6.8 Hz), 2.80 (1H, dd, CH_AH_BPh, J = 13.2, 9.6 Hz), 2.92 (1H, d, OH, J = 3.0 Hz), 3.27 (1H, dd, CH_AH_BPh, J = 13.2, 3.4 Hz), 3.94 (1H, qd, CHCH₃, J = 7.2, 3.0 Hz), 4.23 (2H, m, CH₂O), 4.51 (1H, broad m, CHOH), 4.72 (1H, m, CHN), 5.06 (1H, m, C=CH_AH_B), 5.21 (1H, apparent t, C=CH_AH_B, J = 1.1 Hz), 7.19 – 7.38 (5H, m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 10.2 (CH₃), 21.9 (CH₃), 23.4 (CH₃), 30.4 (CH(CH₃)₂), 37.7 (CH₂Ph), 40.4 (CHCH₃), 55.2 (CHN), 66.2 (CH₂O), 72.3 (CHOH), 108.4 (C=CH₂), 127.5 (phenyl CH), 129.0 (phenyl CH), 135.0 (phenyl CH), 145.7 (OC=O), 154.7 (C=CH₂), 177.4 (NC=O); IR (KBr disc) ν_{max} (cm⁻¹): 3520 (O-H), 1788 (C=O), 1691 (C=O); HRMS m/z (ES) [M+H]⁺ requires 332.1856, found 332.1858

6.2.4 Typical procedure for the synthesis of α-methylene aldehydes

A mixture of aldehyde (1 eq.), formaldehyde (approximately 60% by volume, 37% in H₂O) and dimethylamine hydrochloride (1.2 eq.) was stirred at 70 °C for 24 hours. The reaction was cooled to room temperature and extracted with petrol. The combined organic extracts

were washed with NaHCO_3 and brine, dried (MgSO_4), filtered and concentrated under reduced pressure (care taken as product is volatile).

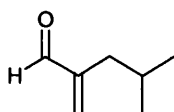
2-Methylene-octanal, 283



According to general procedure 6.2.4, employing octanal (12.18 mL, 0.078 mol), formaldehyde (7.50 mL, 37 % in H_2O) and dimethylamine hydrochloride (7.63 g, 0.094 mol), **2-methylene-octanal 283** (9.40 g, 86%) was prepared as a colourless oil without the need for further purification and with spectroscopic data essentially identical to the literature compound.^[230]

^1H NMR (CDCl_3 , 300 MHz): δ 0.81 (3H, m, CH_3), 1.18 – 1.27 (8H, broad m, C_4H_8), 2.16 (2H, t, $\text{CH}_2\text{C}=\text{CH}_2$, $J = 7.7$ Hz), 5.92 (1H, s, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 6.18 (1H, s, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 9.46 (1H, s, (O)CH); ^{13}C NMR (CDCl_3 , 75 MHz): δ 14.5 (CH_3), 23.00 (CH_2), 26.7 (CH_2), 27.1 (CH_2), 30.4 (CH_2), 30.5 (CH_2), 134.2 ($\text{C}=\text{CH}_2$), 150.9 ($\text{C}=\text{CH}_2$), 195.1 ($\text{C}=\text{O}$); IR (thin film) ν_{max} (cm^{-1}): 1725 ($\text{C}=\text{O}$)

4-Methyl-2-methylene-pentanal, 293



Pyridinium chlorochromate (10.55 g, 48.94 mmol) was added to 4-methyl-pentan-1-ol (2.57 g, 24.47 mmol) in DCM (300 mL) and stirred for 24 hours. The reaction mixture was filtered through fluorosil and celite and evaporated *in vacuo* to yield **4-methyl-pentanal** (2.42 g, 99%) as a colourless liquid which could be used crude in the next reaction.

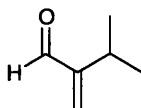
^1H NMR (CDCl_3 , 300 MHz): δ 0.86 (6H, d, $(\text{CH}_3)_2$, $J = 6.7$ Hz), 1.43 – 1.61 (3H, m, CH_2CH), 2.37 (2H, m, CH_2), 9.72 (1H, t, CHO, $J = 1.9$ Hz)

According to general procedure 6.2.4, employing 4-methyl-pentanal (2.42 g, 24.16 mmol), formaldehyde (2.31 mL, 37 % in H_2O) and dimethylamine hydrochloride (3.36 g, 28.99

mmol), **4-methyl-2-methylene-pentanal 293** (2.44 g, 90%) was prepared as a colourless liquid without the need for further purification.

^1H NMR (CDCl_3 , 300 MHz): δ 0.87 (6H, d, $(\text{CH}_3)_2$, $J = 6.8$ Hz), 1.77 (1H, septet, $\text{CH}(\text{CH}_3)_2$, $J = 6.8$ Hz), 2.12 (2H, dd, CH_2 , $J = 7.2, 1.1$ Hz), 6.02 (1H, d, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$, $J = 1.1$ Hz), 6.22 (1H, dd, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$, $J = 1.9, 1.1$ Hz), 9.52 (1H, s, CHO); ^{13}C NMR (CDCl_3 , 75 MHz): δ 22.1 (CH_3), 26.7 (CH), 36.9 (CH_2), 135.1 ($\text{C}=\text{CH}_2$), 156.3 ($\text{C}=\text{CH}_2$), 194.6 ($\text{HC}=\text{O}$); IR (thin film) ν_{max} (cm^{-1}): 1736 ($\text{C}=\text{O}$)

3-Methyl-2-methylene-butyraldehyde, 379



According to general procedure 6.2.4, employing isovaleraldehyde (20 mL, 0.19 mol), formaldehyde (18 mL, 37 % in H_2O) and dimethylamine hydrochloride (18.24 g, 0.23 mol), **3-methyl-2-methylene-butyraldehyde 379** (16.8 g, 90%) was prepared as a colourless oil without the need for further purification and with spectroscopic data essentially identical to the literature compound.^[231]

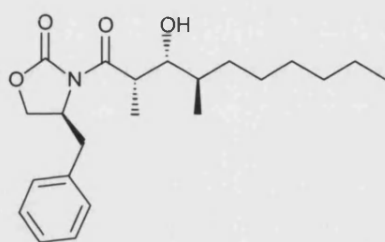
^1H NMR (CDCl_3 , 300 MHz): δ 1.02 (6H, d, $\text{CH}(\text{CH}_3)_2$, $J = 6.8$ Hz), 2.75 (1H, doublet of septets, $\text{CH}(\text{CH}_3)_2$, $J = 6.8, 1.1$ Hz), 5.89 (1H, s, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$), 6.19 (1H, d, $\text{C}=\text{CH}_\text{A}\text{H}_\text{B}$, $J = 1.1$ Hz), 9.48 (1H, s, COH); ^{13}C NMR (CDCl_3 , 75 MHz): δ 20.0 (CH_3), 25.1 (CH), 132.0 ($\text{C}=\text{CH}_2$), 155.1 ($\text{C}=\text{CH}_2$), 193.6 ($\text{C}=\text{O}$); IR (thin film) ν_{max} (cm^{-1}): 1697 ($\text{C}=\text{O}$)

6.2.5 Typical procedure for the asymmetric hydrogenation reaction

A: Using the Endeavour catalyst screening system, unsaturated aldol (1 eq.) was dissolved in DCM in a dry reaction tube and placed in the hydrogenator at 25 °C. The sealed vessel was purged three times with nitrogen before injection of the hydrogenation catalyst in DCM and pressurising with hydrogen to the required pressure. After 24 hours the crude mixture is removed from the hydrogenator and filtered through a plug of silica, washed with methyl *tert*-butyl ether and evaporated *in vacuo*.

B: Using the Parr pressure vessel, unsaturated aldol (1 eq.) was dissolved in DCM and added to the vessel under a nitrogen atmosphere at room temperature. The hydrogenation catalyst in DCM was added under nitrogen before sealing of the vessel and pressurising with hydrogen to the desired pressure. After 24 hours the crude mixture is filtered through a plug of silica, washed with diethyl ether and evaporated *in vacuo*.

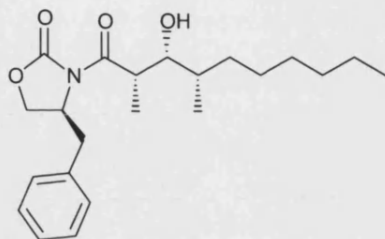
(S)-4-Benzyl-3-((2S,3R,4R)-3-hydroxy-2,4-dimethyl-decanoyl)-oxazolidin-2-one, (4R)-284a



According to general procedure 6.2.5 A or B, employing (S)-4-benzyl-3-((2S,3S)-3-hydroxy-2-methyl-4-methylene-decanoyl)-oxazolidin-2-one **282** (50mg, 0.13 mmol) in DCM (0.5 mL), the crude product is prepared as a pale brown oil. Purification by column chromatography afforded **(S)-4-benzyl-3-((2S,3R,4R)-3-hydroxy-2,4-dimethyl-decanoyl)-oxazolidin-2-one (4R)-284a** as a colourless oil.

$[\alpha]_D^{25} + 15.0^\circ$ (c 0.6, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz): δ 0.82 (6H, m, CH_2CHCH_3 and CH_2CH_3), 1.18 (3H, d, CHCH_3 , $J = 6.8$ Hz), 1.16 – 1.27 (8H, m, $(\text{CH}_2)_4$), 1.50 (1H, m, CH_2CHCH_3), 1.68 (2H, m, CH_2), 2.75 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, $J = 9.4, 4.1$ Hz), 2.87 (1H, d, OH, $J = 3.4$ Hz), 3.20 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, $J = 13.6, 3.4$ Hz), 3.56 (1H, apparent dt, CHOH , $J = 8.7, 2.9$ Hz), 3.91 (1H, qd, CHCH_3 , $J = 6.8, 2.3$ Hz), 4.15 (2H, m, CH_2O , $J = \text{Hz}$), 4.64 (1H, m, CHN), 7.15 (2H, m, Ph), 7.19 – 7.32 (3H, m, Ph); ^{13}C NMR (CDCl_3 , 75 MHz): δ 9.7 (CH_3), 14.1 (CH_3), 15.3 (CH_3), 22.6 (CH_2), 26.7 (CH_2), 29.6 (CH_2), 31.9 (CH_2), 32.6 (CH_2), 35.7 (CH_2CH), 37.7 (CH_2Ph), 39.4 (CHCH_3), 55.1 (CHN), 66.1 (CH_2O), 75.3 (CHOH), 127.4 (phenyl CH), 128.9 (phenyl CH), 129.4 (phenyl CH), 135.00 (phenyl C), 152.8 (OC=O), 178.00 (NC=O); IR (thin film) ν_{max} (cm^{-1}): 3448 (O-H), 1783 (C=O), 1697 (C=O); HRMS: m/z (ES) $[\text{M}+\text{H}]^+$ requires 376.2482, found 376.2483

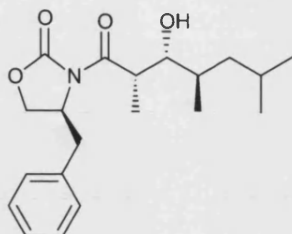
(*S*)-4-Benzyl-3-((2*S*,3*R*,4*S*)-3-hydroxy-2,4-dimethyl-decanoyl)-oxazolidin-2-one, (4*S*)-284b



According to general procedure 6.2.5 A or B, employing (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylene-decanoyl)-oxazolidin-2-one **282** (50 mg, 0.13 mmol) in DCM (0.5 mL), the crude product is prepared as a pale brown oil. Purification by column chromatography afforded (*S*)-4-benzyl-3-((2*S*,3*R*,4*S*)-3-hydroxy-2,4-dimethyl-decanoyl)-oxazolidin-2-one (4*S*)-**284b** as a colourless oil.

$[\alpha]_D^{25}$ - 22.5 ° (c 0.4, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 0.88 (3H, m, CH₂CH₃), 0.97 (3H, d, CH₂CHCH₃, J = 6.4 Hz), 1.26 (3H, d, CHCH₃, J = 6.8 Hz), 1.22 – 1.40 (9H, m, CH(CH₂)₄), 1.57 (2H, m, CH₂), 2.60 (1H, d, OH, J = 3.8 Hz), 2.79 (1H, dd, CH_AH_BPh, J = 9.4, 13.2 Hz), 3.26 (1H, dd, CH_AH_BPh, J = 13.2, 3.2 Hz), 3.68 (1H, apparent pentet, CHOH, J = 3.8 Hz), 3.99 (1H, qd, CHCH₃, J = 6.8, 3.8 Hz), 4.20 (2H, m, CH₂O), 4.69 (1H, m, CHN), 7.21 (2H, m, Ph), 7.25 – 7.37 (3H, m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 11.2 (CH₃), 14.1 (CH₃), 15.1 (CH₃), 22.6 (CH₂), 26.8 (CH₂), 29.5 (CH₂), 31.8 (CH₂), 32.9 (CH₂), 35.6 (CH₂CHCH₃), 37.8 (CH₂Ph), 39.9 (CHCH₃), 55.1 (CHN), 66.1 (CH₂O), 75.3 (CHOH), 127.4 (phenyl CH), 129.0 (phenyl CH), 129.4 (phenyl CH), 135.0 (phenyl C), 152.9 (OC=O), 177.6 (NC=O); IR and mass spec data identical to (*S*)-4-Benzyl-3-((2*S*,3*R*,4*R*)-3-hydroxy-2,4-dimethyl-decanoyl)-oxazolidin-2-one (4*R*)-**284a**

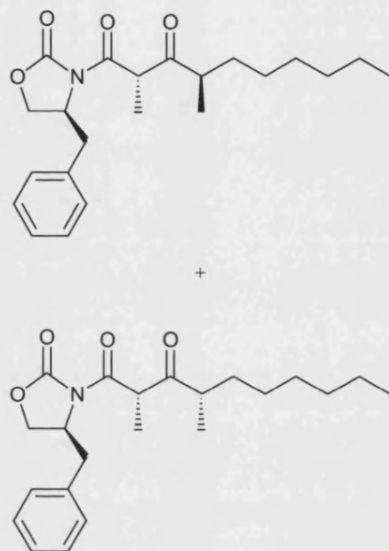
(*S*)-4-Benzyl-3-((2*S*,3*R*,4*R*)-3-hydroxy-2,4,6-trimethyl-heptanoyl)-oxazolidin-2-one, **291a**



According to general procedure 6.2.5 B, employing (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2,6-dimethyl-4-methylene-heptanoyl)-oxazolidin-2-one **292** (200 mg, 0.58 mmol) in DCM (2 mL), Wilkinson's catalyst (93.7 mg, 0.10 mmol) in DCM (2 mL) and 5 bar hydrogen pressure, the crude product was prepared in 33% *d.e.* after 24 hours as a light brown oil. Purification by column chromatography afforded (*S*)-4-benzyl-3-((2*S*,3*R*,4*R*)-3-hydroxy-2,4,6-trimethyl-heptanoyl)-oxazolidin-2-one **291a** as a pale yellow oil.

$[\alpha]_D^{25} + 17.4^\circ$ (c 1.0, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz): δ 0.84 (3H, d, $\text{CH}(\text{CH}_3)_2$, $J = 4.7$ Hz), 0.86 (3H, d, $\text{CH}(\text{CH}_3)_2$, $J = 4.7$ Hz), 0.92 (3H, d, CHCH_3 , $J = 6.4$ Hz), 1.25 (3H, d, $\text{C}=\text{OCHCH}_3$, $J = 7.2$ Hz), 1.49 – 1.73 (4H, overlapping multiplets, CHCH_3 , CH_2 -*i*Pr, $\text{CH}(\text{CH}_3)_2$), 2.79 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, $J = 13.2, 9.4$ Hz), 3.26 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, $J = 13.2, 3.4$ Hz), 3.58 (1H, apparent dt, CHOH , $J = 7.9, 3.4$ Hz), 3.98 (1H, qd, $\text{C}=\text{OCHCH}_3$, $J = 7.2, 2.6$ Hz), 4.21 (2H, m, CH_2O), 4.69 (1H, m, CHN), 7.19 – 7.38 (5H, m, Ph); ^{13}C NMR (CDCl_3 , 75 MHz): δ 10.2 (CH_3), 15.5 (CH_3), 21.3 (CH_3), 24.3 (CH_3), 25.3 ($\text{CH}(\text{CH}_3)_2$), 33.5 (CHCH_3), 37.7 (CH_2 -*i*Pr), 39.6 ($\text{C}=\text{OCHCH}_3$), 42.0 (CH_2Ph), 55.2 (CHN), 66.1 (CH_2O), 76.1 (CHOH), 127.4 (phenyl CH), 129.0 (phenyl CH), 129.4 (phenyl CH), 135.0 (phenyl C), 152.8 ($\text{OC}=\text{O}$), 177.8 ($\text{NC}=\text{O}$); IR (thin film) ν_{max} (cm^{-1}): 3540 (O-H), 1792 ($\text{C}=\text{O}$), 1689 ($\text{C}=\text{O}$); HRMS: m/z (ES) $[\text{M}+\text{H}]^+$ requires 348.2169, found 348.2173

(*S*)-1-((*S*)-4-Benzyl-2-oxo-oxazolidin-3-yl)-2,4-dimethyl-decane-1,3-dione, **286 and *ent*-**286****



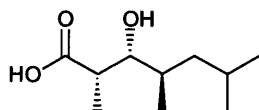
286 and *ent*-286

According to general procedure 6.2.5 A or B, employing (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylene-decanoyl)-oxazolidin-2-one **282** (50 mg, 0.13 mmol) in DCM (0.5 mL), the crude product is prepared as a pale brown oil. Purification by column chromatography afforded (*S*)-1-((*S*)-4-benzyl-2-oxo-oxazolidin-3-yl)-2,4-dimethyl-decane-1,3-dione **286** and *ent*-**286** as a 84:16 mixture of diastereomers.

¹H NMR (CDCl₃, 300 MHz): δ 0.82 (6H, m, **286** CH₂CH₃ and *ent*-**286** CH₂CH₃), 1.05 (3H, d, **286** CH₃, J = 6.8 Hz), 1.08 (3H, d, *ent*-**286** CH₃, J = 7.2 Hz), 1.11 (3H, d, **286** CH₃, J = 7.2 Hz), 1.16 (3H, d, *ent*-**286** CH₃, J = 7.2 Hz), 1.18 – 1.28 (16H, broad m, **286** C₄H₈ and *ent*-**286** C₄H₈), 1.38 (1H, apparent d, *ent*-**286** C=OCHCH_AH_B, J = 2.3 Hz), 1.40 (1H, apparent d, **286**, C=OCHCH_AH_B, J = 2.6 Hz), 1.41 (1H, apparent d, *ent*-**286** C=OCHCH_AH_B, J = 2.3 Hz), 1.42 (1H, apparent d, **286** C=OCHCH_AH_B, J = 2.3 Hz), 2.70 (4H, overlapping m, **286** CH_AH_BPh and C=OCHCH₂ and *ent*-**286** CH_AH_BPh and C=OCHCH₂), 3.25 (1H, dd, **286** CH_AH_BPh, J = 13.2, 3.0 Hz), 3.43 (1H, dd, *ent*-**286** CH_AH_BPh, J = 13.2, 3.0 Hz), 4.15 (4H, overlapping m, **286** CH₂O and *ent*-**286** CH₂O), 4.69 (2H, overlapping m, **286** CHN and *ent*-**286** CHN), 4.84 (2H, overlapping m, **286** CHCH₃ and *ent*-**286** CHCH₃), 7.13 – 7.32 (10H, m, **286** Ph and *ent*-**286** Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 13.0 (CH₃), 14.1 (CH₃), 16.1 (CH₃), 22.6 (CH₂), 27.0 (CH₂), 29.2

(CH₂), 31.7 (CH₂), 32.6 (CH₂), 37.9 (CH₂Ph), 44.3 (C=OCHCH₂), 51.7 (CH), 55.3 (CH), 66.3 (CH₂O), 127.3 (phenyl CH), 128.9 (phenyl CH), 129.4 (phenyl CH), 135.5 (phenyl C), 153.5 (OC=O), 170.7 (NC=O), 211.2 (CHC=O) all peaks exhibit a smaller corresponding peak for **ent-286**; IR (thin film) ν_{\max} (cm⁻¹): 1782 (C=O), 1716 (C=O), 1697 (C=O); HRMS: m/z (ES) [M+H]⁺ requires 374.2326, found 374.2329

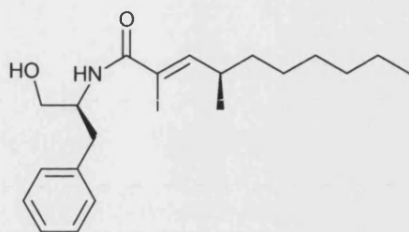
6.2.6 Procedure for the synthesis of (2*S*,3*R*,4*R*)-3-hydroxy-2,4,6-trimethyl-heptanoic acid, **290a**



(*S*)-4-Benzyl-3-((2*S*,3*R*,4*R*)-3-hydroxy-2,4,6-trimethyl-heptanoyl)-oxazolidin-2-one **291a** (12 mg, 0.04 mmol) in 3:1 THF:H₂O (0.8 mL) at 0 °C was treated with H₂O₂ (0.02 mL, 35% solution, 0.24 mmol) followed by LiOH (1.7 mg, 0.08 mmol). The reaction was stirred at 0 °C for 3 hours and the excess peracid was quenched with a 10% excess of Na₂SO₃ (28.7 mg) dissolved in water. The mixture was buffered to pH 9 – 10 with NaHCO₃ and the solvent removed *in vacuo*. Extraction with DCM removes oxazolidin-2-one **276**, and the aqueous layer was acidified to pH 1 – 2 with 1M HCl before extraction with ethyl acetate. The combined organic extracts were dried (MgSO₄), filtered and evaporated *in vacuo* to afford (2*S*,3*R*,4*R*)-3-hydroxy-2,4,6-trimethyl-heptanoic acid **290a** (7 mg, 97%) as a colourless oil with spectroscopic data essentially identical to the literature compound.^[193]

$[\alpha]_D^{25} + 8.6^\circ$ (c 0.47, CHCl₃) [lit. + 24.4 ° (c 1.00, CHCl₃)]; ¹H NMR (CDCl₃, 300 MHz): δ 0.83 (3H, d, CH(CH₃)₂, J = 6.8 Hz), 0.84 (3H, d, CHCH₃, J = 6.4 Hz), 0.91 (3H, d, CH(CH₃)₂, J = 6.8 Hz), 1.04 (2H, m, CH₂), 1.21 (3H, d, C=OCHCH₃, J = 7.2 Hz), 1.49 (1H, m, CH(CH₃)₂), 1.64 (1H, m, CHCH₃), 2.72 (1H, qd, C=OCHCH₃, J = 7.2, 3.4 Hz), 3.65 (1H, dd, CHOH, J = 7.9, 3.4 Hz); ¹³C NMR (CDCl₃, 75 MHz): δ 9.9 (CH₃), 14.1 (CH₃), 21.0 (CH(CH₃)₂), 21.2 (CH(CH₃)₂), 25.2 (CH(CH₃)₂), 30.9 (CHCH₃), 41.6 (CH₂), 50.8 (C=OCHCH₃), 76.2 (CHOH), 180.9 (C=O); IR (thin film) ν_{\max} (cm⁻¹): 1710 (C=O)

6.2.7 Procedure for the synthesis of (*E*)-(*R*)-2,4-dimethyl-dec-2-enoic acid ((*S*)-1-benzyl-2-hydroxy-ethyl)-amide, 302



LHMDS (0.076 mL, 1 M solution, 0.076 mmol) was added to (*S*)-4-benzyl-3-((2*S*,3*R*,4*R*)-3-hydroxy-2,4-dimethyl-decanoyl)-oxazolidin-2-one (*4R*)-**284a** (26 mg, 0.069 mmol) in toluene (1.5 mL) at 0 °C. After stirring for 2 hours at 0 °C the reaction was quenched with a few drops of pH 7 buffer, dried (MgSO₄), filtered and evaporated *in vacuo* to yield the crude product as a yellow oil. Purification by column chromatography afforded (*E*)-(*R*)-2,4-dimethyl-dec-2-enoic acid ((*S*)-1-benzyl-2-hydroxy-ethyl)-amide **302** (23 mg, 99%) as a colourless oil.

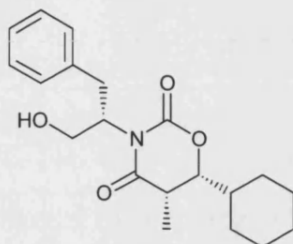
$[\alpha]_D^{25} - 36.6^\circ$ (c 0.57, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 0.87 (3H, t, CH₂CH₃, J = 6.8 Hz), 0.93 (3H, d, CHCH₃, J = 6.4 Hz), 1.17 – 1.32 (10H, m, (CH₂)₅), 1.76 (3H, d, CH=CCH₃, J = 1.5 Hz), 2.39 (1H, m, CHCH₃), 2.91 (2H, apparent qd, CH_AH_BPh, J = 13.6, 7.1 Hz), 3.28 (1H, broad s, OH), 3.64 (1H, dd, CH_AH_BOH, J = 10.9, 5.7 Hz), 3.75 (1H, dd, CH_AH_BOH, J = 10.9, 3.4 Hz), 4.17 (1H, m, CHNH), 5.88 (1H, broad d, NH, J = 6.8 Hz), 5.97 (1H, dd, CH=C, J = 9.8, 1.1 Hz), 7.19 – 7.35 (5H, m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 12.7 (CH₃), 14.1 (CH₃), 17.4 (CH₂), 20.2 (CH₃), 22.6 (CH₂), 27.4 (CH₂), 29.4 (CH₂), 31.8 (CH₂), 32.9 (CHCH₃), 36.9 (CH₂Ph), 53.6 (CHNH), 65.1 (CH₂OH), 126.8 (phenyl CH), 128.7 (phenyl CH), 129.2 (phenyl CH), 135.3 (C), 137.6 (C), 143.2 (CH=C), 170.5 (C=O); IR (thin film) ν_{\max} (cm⁻¹): 3348 (O-H), 1659 (C=O); HRMS: m/z (ES) [M+H]⁺ requires 332.2584, found 332.2586

6.2.8 Typical procedure for the diethyl zinc rearrangement reaction

A solution of diethyl zinc (1.0 M, 0.1 eq.) in toluene was added dropwise to a stirred solution of the *syn*-aldol (1 eq.) in DCM at room temperature. After 2 hours the reaction was quenched with saturated NH₄Cl and the organics extracted with DCM. The combined

organic extracts were washed with brine, dried (MgSO_4) and concentrated *in vacuo* to afford the crude product.

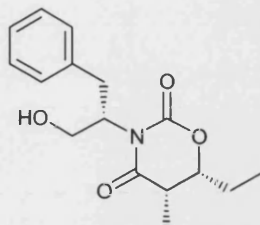
(5*S*,6*R*)-3-((*S*)-1-Benzyl-2-hydroxy-ethyl)-6-cyclohexyl-5-methyl-[1,3]oxazinane-2,4-dione, 312



According to general procedure 6.2.8, employing (*S*)-4-benzyl-3-((2*S*,3*R*)-3-cyclohexyl-3-hydroxy-2-methyl-propionyl)-oxazolidin-2-one **306** (0.10 g, 0.29 mmol) and diethyl zinc (0.029 mL, 1 M solution, 0.029 mmol), the crude product was prepared as a colourless oil. Purification by column chromatography afforded **(5*S*,6*R*)-3-((*S*)-1-benzyl-2-hydroxy-ethyl)-6-cyclohexyl-5-methyl-[1,3]oxazinane-2,4-dione 312** (0.09 g, 94%) as a colourless oil.

$[\alpha]_D^{25}$ - 17.0 ° (c 1.00, CH_2Cl_2); ^1H NMR (300MHz, CDCl_3): δ 0.59 – 0.81 (2H, m, *cyclohexyl*), 0.82 (3H, d, CH_3CH , $J = 7.2$ Hz), 1.06 – 1.20 (3H, m, *cyclohexyl*), 1.29 – 1.38 (1H, m, *cyclohexyl*), 1.41 – 1.49 (1H, m, *cyclohexyl*), 1.55 – 1.69 (3H, m, *cyclohexyl*), 2.04 (1H, apparent d, *cyclohexyl*, $J = 13.2$ Hz), 2.47 (1H, qd, CHCH_3 , $J = 7.5, 2.6$ Hz), 2.99 (1H, dd, PhCH_ACH_B , $J = 13.9, 6.4$ Hz), 3.12 (1H, dd, PhCH_ACH_B , $J = 13.9, 10.6$ Hz), 3.23 (1H, obscured m, CH-cyclohexyl) 3.81 (1H, dd, $\text{CH}_A\text{H}_B\text{OH}$, $J = 11.7, 3.8$ Hz), 3.99 (1H, dd, $\text{CH}_A\text{H}_B\text{OH}$, $J = 11.7, 7.5$ Hz), 5.01 (1H, apparent ddt, CHN , $J = 13.9, 6.8, 3.4$ Hz), 7.08 – 7.23 (5H, m, Ph); ^{13}C NMR (75MHz, CDCl_3): δ 9.4 (CH_3), 25.4 (CH_2), 26.3 (CH_2), 27.5 (CH_2), 29.6 (CH_2), 33.9 (CH_2Ph), 37.2 (CH) 38.1 (CH), 56.5 (CHN), 63.8 (CH_2OH), 81.1 (CHO), 127.1 (phenyl CH), 128.9 (phenyl CH), 129.5 (phenyl CH), 137.9 (phenyl C), 152.4 (C=O), 174.2 (C=O); IR (thin film) ν_{max} (cm^{-1}): 3396 (broad, OH), 1747 (C=O), 1690 (C=O); HRMS m/z (ES) $[\text{M}+\text{H}]^+$ requires 346.2013, found 346.2015

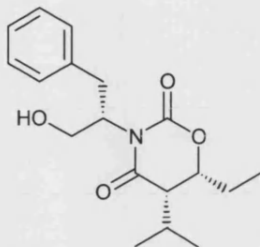
(5*S*,6*R*)-3-((*S*)-1-Benzyl-2-hydroxy-ethyl)-6-ethyl-5-methyl-[1,3]oxazinane-2,4-dione, 313



According to general procedure 6.2.8, employing (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methyl-pentanoyl)-oxazolidin-2-one **280** (0.10 g, 0.34 mmol) and diethyl zinc (0.034 mL, 1 M solution, 0.034 mmol) the crude product was prepared as a colourless oil. Purification by column chromatography afforded **(5*S*,6*R*)-3-((*S*)-1-benzyl-2-hydroxy-ethyl)-6-ethyl-5-methyl-[1,3]oxazinane-2,4-dione 313** (0.093 g, 94%) as a colourless oil.

$[\alpha]_D^{25}$ - 6.4 ° (c 0.47, CH₂Cl₂); ¹H NMR (300MHz, CDCl₃): δ 0.82 (3H, t, CH₂CH₃, J = 7.5 Hz), 0.99 (3H, d, CH₃CH, J = 7.2 Hz), 1.33 (2H, m, CH₂CH₃), 2.50 (1H, qd, CHCH₃, J = 7.5, 3.4 Hz), 2.99 (1H, dd, PhCH_ACH_B, J = 13.9, 6.4 Hz), 3.16 (1H dd, PhCH_ACH_B, J = 13.9, 10.5 Hz), 3.68 (1H, obscured m, CH-CH₂CH₃), 3.82 (1H, dd, CH_AH_BOH, J = 11.7, 3.8 Hz), 4.01 (1H, dd, CH_AH_BOH, J = 11.7, 7.7 Hz), 5.04 (1H, app ddt, CHN, J = 13.9, 6.8, 3.4 Hz), 7.10 – 7.15 (5H, m, Ph). ¹³C NMR (75MHz, CDCl₃): δ 9.2 (CH₃), 9.5 (CH₃), 22.6 (CH₂CH₃), 33.7 (CH₂Ph), 39.2 (CHCH₃), 56.5 (CHN), 63.3 (CH₂OH), 78.4 (CHO), 126.6 (phenyl CH), 128.5 (phenyl CH), 129.1 (phenyl CH), 137.4 (phenyl C), 151.8 (C=O), 173.1 (C=O); IR (thin film) ν_{\max} (cm⁻¹): 3462 (broad, OH), 1755 (C=O), 1700 (C=O); HRMS m/z (ES) [M+H]⁺ requires 292.1543, found 292.1547

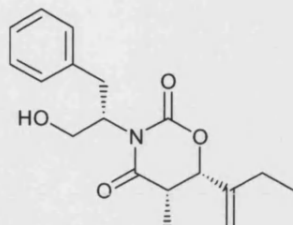
(5*S*,6*R*)-3-((*S*)-1-Benzyl-2-hydroxy-ethyl)-6-ethyl-5-isopropyl-[1,3]oxazinane-2,4-dione, 314



According to general procedure 6.2.8, employing (*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-isopropyl-pentanoyl)-oxazolidin-2-one **307** (0.1 g, 0.31 mmol) and diethyl zinc (0.031 mL, 1 M solution, 0.031 mmol), the crude product was prepared a pale yellow oil. Purification by column chromatography afforded **(5*S*,6*R*)-3-((*S*)-1-benzyl-2-hydroxy-ethyl)-6-ethyl-5-isopropyl-[1,3]oxazinane-2,4-dione 314** (0.089 g, 90%) as a colourless oil.

$[\alpha]_D^{25}$ - 6.8 ° (c 0.59, CH₂Cl₂); ¹H NMR (300MHz, CDCl₃): δ 0.84 (3H, t, CH₂CH₃, J = 7.5 Hz), 0.85 (3H, d, CH(CH₃)₂, J = 7.0 Hz), 0.92 (3H, d, CH(CH₃)₂, J = 7.0 Hz), 1.31 – 1.46 (1H, dqd, CH_AH_BCH₃, J = 14.0, 7.5, 5.0 Hz), 1.45 – 1.61 (1H, m, CH_AH_BCH₃), 1.94 – 2.05 (1H, m, CH(CH₃)₂), 2.18 (1H, apparent t, CH-^{*i*}Pr, J = 4.5 Hz), 2.53 (1H, broad s, OH), 2.99 (1H, dd, CH_AH_BPh, J = 14.0, 7.0 Hz), 3.13 (1H, dd, CH_ACH_BPh, J = 14.0, 10.5 Hz), 3.64 (1H, obscured m, CHO), 3.82 (1H, dd, CH_AH_BOH, J = 12.0, 4.0 Hz), 4.02 (1H, dd, CH_ACH_BOH, J = 12.0, 7.0 Hz), 5.04 – 5.14 (1H, apparent dtd, CHN, J = 10.5, 7.0, 4.0 Hz), 7.08 – 7.22 (5H, m, Ph); ¹³C NMR (75MHz, CDCl₃): δ 10.4 (CH₃), 20.2 (CH₃), 22.6 (CH₃), 23.4 (CH₂CH₃), 25.5 (CH(CH₃)₂), 34.3 (CH₂Ph), 50.2 (CH-^{*i*}Pr), 56.5 (CHN), 63.7 (CH₂OH), 79.4 (CHO), 127.0 (phenyl CH), 128.9 (phenyl CH), 129.5 (phenyl CH), 135.0 (phenyl C), 152.5 (OC=O), 171.4 (NC=O); IR (thin film) ν_{max} (cm⁻¹): 3423 (broad OH), 1754 (C=O), 1691 (C=O); HRMS m/z (ES) [M+H]⁺ requires 320.1857, found 320.1861

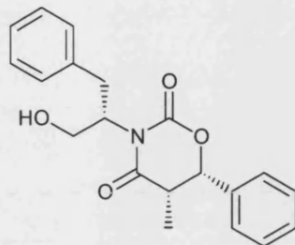
(5*S*,6*S*)-3-((*S*)-1-Benzyl-2-hydroxy-ethyl)-5-methyl-6-(1-methylene-propyl)-[1,3]oxazinane-2,4-dione, 315



According to general procedure 6.2.8, employing (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylene-hexanoyl)-oxazolidin-2-one **308** (0.1 g, 0.32 mmol) and diethyl zinc (0.32 mL, 1 M solution, 0.32 mmol), the crude product was prepared as a colourless oil. Purification by column chromatography afforded **(5*S*,6*S*)-3-((*S*)-1-benzyl-2-hydroxy-ethyl)-5-methyl-6-(1-methylene-propyl)-[1,3]oxazinane-2,4-dione 315** (0.061 g, 60%) as a colourless oil.

$[\alpha]_D^{25}$ - 49.0 ° (c 0.59, CHCl₃); ¹H NMR (300MHz, CDCl₃): δ 0.99 (6H, overlapping m, CH₂CH₃ and CHCH₃), 1.83 (2H, overlapping m, CH₂CH₃), 2.60 (1H, qd, CHCH₃, J = 7.5, 3.0 Hz), 3.07 (1H, dd, CH_AH_BPh, J = 13.9, 6.4 Hz), 3.22 (1H, dd, CH_AH_BPh, J = 13.9, 10.5 Hz), 3.90 (1H, dd, CH_AH_BOH, J = 11.9, 4.0 Hz), 4.10 (1H, dd, CH_AH_BOH, J = 11.9, 7.4 Hz), 4.21 (1H, apparent s, CHO), 5.08 (1H, s, C=CH_AH_B), 5.13 (1H, m, CHN), 5.22 (1H, s, C=CH_AH_B), 7.16 – 7.31 (5H, m, Ph); ¹³C NMR (75MHz, CDCl₃): δ 9.7 (CH₃), 12.0 (CH₃), 25.4 (CH₂CH₃), 33.9 (CH₂Ph), 38.8 (CHCH₃), 56.7 (CHN), 63.8 (CH₂OH), 77.6 (CHO), 112.1 (C=CH₂), 127.1 (phenyl CH), 128.9 (phenyl CH), 129.8 (phenyl CH), 137.8 (C), 142.4 (C), 151.8 (OC=O), 173.7 (NC=O); IR (thin film) ν_{max} (cm⁻¹): 3441 (O-H), 1751 (C=O), 1694 (C=O); HRMS m/z (ES) [M+H]⁺ requires 318.1700, found 318.1692

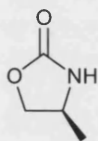
(5*S*,6*S*)-3-((*S*)-1-Benzyl-2-hydroxy-ethyl)-5-methyl-6-phenyl-[1,3]oxazinane-2,4-dione, 316



According to general procedure 6.2.8, employing (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-3-phenyl-propionyl)-oxazolidin-2-one **309** (0.1 g, 0.29 mmol) and diethyl zinc (0.029 mL, 1 M solution, 0.029 mmol), the crude product was prepared as a yellow oil. Purification by column chromatography afforded **(5*S*,6*S*)-3-((*S*)-1-benzyl-2-hydroxy-ethyl)-5-methyl-6-phenyl-[1,3]oxazinane-2,4-dione 316** (0.035 g, 35%) as a yellow oil.

$[\alpha]_D^{25}$ - 59.0 ° (c 0.48, CHCl₃); ¹H NMR (300MHz, CDCl₃): δ 0.91 (3H, d, CH₃, J = 7.5 Hz), 1.66 (1H, broad s, OH), 2.72 (1H, qd, CHCH₃, J = 7.5, 3.0 Hz), 3.10 (1H, dd, CH_AH_BPh, J = 13.9, 6.4 Hz), 3.26 (1H, dd, CH_AH_BPh, J = 13.9, 10.9 Hz), 3.94 (1H, dd, CH_AH_BOH, J = 11.7, 4.1 Hz), 4.15 (1H, dd, CH_AH_BOH, J = 11.7, 7.9 Hz), 4.97 (1H, apparent s, CHO), 5.19 (1H, m, CHN), 7.19 – 7.40 (10H, m, Ph); ¹³C NMR (75MHz, CDCl₃): δ 9.9 (CH₃), 34.0 (CH₂Ph), 42.0 (CHCH₃), 63.8 (CH₂OH), 77.8 (CHO), 125.8 (phenyl CH), 127.2 (phenyl CH), 128.9 (phenyl CH), 129.1 (phenyl CH), 129.4 (phenyl CH), 129.5 (phenyl CH), 134.4 (phenyl C), 137.8 (phenyl C), 153.2 (OC=O), 173.6 (NC=O); IR (thin film) ν_{\max} (cm⁻¹): 3449 (O-H), 1755 (C=O), 1697 (C=O); HRMS *m/z* (ES) [M+H]⁺ requires 340.1543, found 340.1545

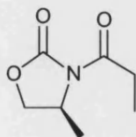
6.2.9 Procedure for the synthesis of (*S*)-4-methyl-oxazolidin-2-one, **322**



Diethyl carbonate (19.0 mL, 157.80 mmol) was added to (*S*)-alaninol (5.75 g, 76.6 mmol), immediately followed by the addition of potassium carbonate (1.06 g, 7.66 mmol) in one portion to a three-necked flask fitted with standard distillation equipment. The reaction was stirred for 10 minutes then heated to 135 °C for 6 hours, or until ethanol ceased to distil from the reaction. The reaction was quenched with saturated aqueous ammonium chloride solution and the organics extracted with ether. The combined organic extracts were washed with brine, dried (MgSO₄) and the solvent evaporated *in vacuo* to afford the crude product. Recrystallisation in diethyl ether/hexane afforded (*S*)-4-methyl-oxazolidin-2-one **322** (6.58 g, 85%) as a white solid, with spectroscopic data essentially identical to the literature compound.^[232]

mp 42 – 44 °C [lit. 45.9 °C]; $[\alpha]_D^{25} + 11.0^\circ$ (c 1.32, CHCl₃) [lit. 8.1 (c 2.00, CHCl₃)]; ¹H NMR (300MHz, CDCl₃): δ 1.24 (3H, d, J = 6.0 Hz, CH₃CH), 3.89 (1H, dd, OCH_AH_B, J = 8.5, 6.5 Hz), 3.96 (1H, m, OCH_AH_B), 4.47 (1H, m, CHCH₃), 6.53 (1H, broad s, NH); ¹³C NMR (75MHz, CDCl₃): δ 21.5 (CH₃), 49.2 (CHCH₃), 72.6 (CH₂), 161.1 (C=O); IR (KBr disc) ν_{max} (cm⁻¹): 3256 (broad N-H), 1745 (C=O)

6.2.10 Procedure for the synthesis of (*S*)-4-methyl-3-propionyloxazolidin-2-one, **323**



n-BuLi (4.40 mL, 2.5 M solution in hexanes, 10.98 mmol) was added to a solution of (*S*)-4-methyloxazolidin-2-one **322** (1.10 g, 10.88 mmol) in THF (40 mL) at -78 °C and stirred for 30 minutes. Propionyl chloride (1.04 mL, 11.97 mmol) was then added dropwise over 5

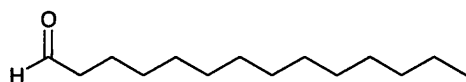
minutes and stirred for a further two hours whilst warming to 0 °C. The reaction was quenched with aqueous saturated ammonium chloride solution and allowed to warm to room temperature, diluted with ether (20 mL), washed with aqueous saturated sodium hydrogen carbonate solution, sufficient to dissolve the white precipitate. The organics were extracted with ethyl acetate, dried (MgSO₄) and the solvent removed *in vacuo* to give the crude product. Purification by column chromatography afforded **(S)-4-methyl-3-propionyloxazolidin-2-one 323** (1.33 g, 78%) as a yellow oil.

$[\alpha]_D^{25} + 81.0^\circ$ (c 1.21, CH₂Cl₂); ¹H NMR (300MHz, CDCl₃): δ 1.15 (3H, t, CH₃CH₂, J = 7.0 Hz), 1.41 (3H, d, CH₃CH, J = 6.0 Hz), 2.95 – 2.86 (2H, apparent td, CH₂CH₃, J = 7.0, 2.5 Hz), 3.97 (1H, dd, OCH_AH_B, J = 8.5, 3.0 Hz), 4.41 (1H, apparent t, OCH_AH_B, J = 8.5 Hz), 4.55 (1H, m, CHN); ¹³C NMR (75MHz, CDCl₃): δ 8.7 (CH₃), 19.7 (CH₃), 29.6 (CH₂CH₃), 50.8 (CHCH₃), 69.5 (CH₂O), 154.0 (OC=O), 174.4 (NC=O); IR (thin film) ν_{max} (cm⁻¹): 1775 (C=O), 1702 (C=O); HRMS: m/z (ES) [M+H]⁺ requires 158.0812, found 158.0812

6.2.11 Typical procedure for the pyridinium chlorochromate oxidation of alcohols to aldehydes

Pyridinium chlorochromate (2 eq.) was added to the primary alcohol (1 eq.) in DCM and stirred for 3 hours. The reaction mixture was filtered through fluorosil and celite and evaporated *in vacuo* to yield the product which could be used crude in subsequent reactions.

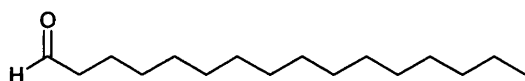
Tetradecanal, 324



According to general procedure 6.2.11, employing 1-tetradecanol (0.5 g, 2.33 mmol) in DCM (60 mL) and pyridinium chlorochromate (1.00 g, 4.66 mmol), **tetradecanal 324** (0.49 g, 97%) was prepared as a viscous oil, with spectroscopic data essentially identical to the literature compound.^[233]

^1H NMR (300MHz, CDCl_3): δ 0.88 (3H, t, $J = 8.5$ Hz, CH_3), 1.35 (20H, m, $\text{C}_{10}\text{H}_{20}$), 1.55 (2H, m, CH_2), 2.41 (2H, td, $J = 7.0, 2.0$ Hz, CHOCH_2), 9.76 (1H, t, $J = 2.0$ Hz, CHO); ^{13}C NMR (75MHz, CDCl_3): δ 14.5 (CH_3), 22.5 (CH_2), 23.1 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 29.9 (CH_2), 30.0 (CH_2), 30.1 (CH_2), 32.3 (CH_2), 44.3 (CH_2), 203.4 (HCO); IR (thin film) ν_{max} (cm^{-1}): 1728 (C=O)

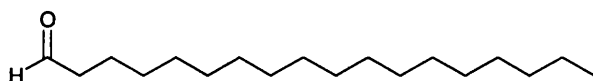
Hexadecanal, 325



According to general procedure 6.2.11, employing 1-hexadecanol (0.5 g, 2.06 mmol) in DCM (60 mL) and pyridinium chlorochromate (0.89 g, 4.12 mmol), **hexadecanal 325** (0.48 g, 99%) was prepared as an off white solid which could be used crude in subsequent reactions.

mp 40 – 41 °C; ^1H NMR (300MHz, CDCl_3): δ 0.87 (3H, t, $J = 8.5$ Hz, CH_3), 1.35 (24H, m, $\text{C}_{12}\text{H}_{24}$), 1.53 (2H, m, CH_2), 2.37 (2H, td, $J = 7.0, 2.0$ Hz, CHOCH_2), 9.72 (1H, t, $J = 2.0$ Hz, CHO); ^{13}C NMR (75MHz, CDCl_3): δ 14.5 (CH_3), 22.5 (CH_2), 23.1 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 29.9 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 30.1 (CH_2), 30.1 (CH_2), 32.3 (CH_2), 44.3 (CH_2), 203.4 (HCO); IR (KBr disc) ν_{max} (cm^{-1}): 1726 (C=O)

Octadecanal, 326



According to general procedure 6.2.11, employing 1-octadecanol (0.5 g, 1.85 mmol) in DCM (60 mL) and pyridinium chlorochromate (0.79 g, 3.70 mmol), **octadecanal 326** (0.47 g, 96%) was prepared as an off white solid which could be used crude in subsequent reactions.

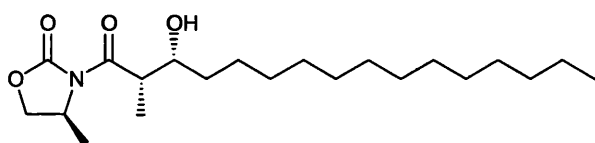
mp 57 – 58 °C; ^1H NMR (300MHz, CDCl_3): δ 0.88 (3H, t, $J = 8.5$ Hz, CH_3), 1.35 (28H, m, $\text{C}_{14}\text{H}_{28}$), 1.55 (2H, m, CH_2), 2.38 (2H, td, $J = 7.0, 2.0$ Hz, CHOCH_2), 9.71 (1H, t, $J = 2.0$ Hz, CHO); ^{13}C NMR (75MHz, CDCl_3): δ 14.5 (CH_3), 22.5 (CH_2), 23.1 (CH_2), 29.6 (CH_2),

29.8 (CH₂), 29.8 (CH₂), 29.9 (CH₂), 30.0 (CH₂), 30.0 (CH₂), 30.1 (CH₂), 30.1 (CH₂), 32.3 (CH₂), 44.3 (CH₂), 203.3 (HCO); IR (KBr disc) ν_{\max} (cm⁻¹): 1728 (C=O)

6.2.12 Typical procedure for the (*S*)-4-methyl-oxazolidin-2-one mediated *syn*-aldol reaction

A solution of *N*-acylated 4-methyl-oxazolidinone (1 eq.) in DCM was cooled to 0 °C in an ice bath and 9-BBNOTf (1.1 eq., 0.5 M solution in hexanes) added dropwise. The mixture was left stirring for 30 min at 0 °C before addition of diisopropylethylamine (1.3 eq.) and stirring for a further 40 min. The reaction was then cooled to – 78 °C in an acetone-dry ice bath before addition of the aldehyde (1.1 eq.) in DCM and stirring for 1 hr at – 78 °C followed by 1 hr at 0 °C. The mixture was allowed to warm to room temperature, pH 7 phosphate buffer added and stirred for 5 min before addition of 2:1 hydrogen peroxide:methanol (v/v) and stirring for 16 hrs. The bulk of the solvent was removed *in vacuo* and the resulting slurry partitioned between water and diethyl ether. The combined organic extracts were washed with 5 % Na₂CO₃ and brine, dried (MgSO₄), filtered and evaporated *in vacuo*.

(*S*)-3-((2*S*,3*R*)-3-Hydroxy-2-methyl-hexadecanoyl)-4-methyl-oxazolidin-2-one, 327

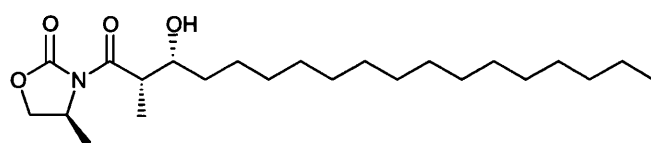


According to general procedure 6.2.12, employing (*S*)-4-methyl-3-propionyloxazolidin-2-one **323** (0.13 g, 0.83 mmol) in DCM (6 mL), 9-BBNOTf (1.82 mL, 0.5 M, 0.91 mmol), diisopropylethylamine (0.19 mL, 1.08 mmol) and tetradecanal **324** (0.19 g, 0.91 mmol) in DCM (2.5 mL), the crude product was prepared as a dark yellow oil. Purification by column chromatography afforded (*S*)-3-((2*S*,3*R*)-3-hydroxy-2-methyl-hexadecanoyl)-4-methyl-oxazolidin-2-one **327** (0.25 g, 81%) as a yellow oil.

$[\alpha]_D^{25} + 40.0^\circ$ (c 0.60, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 0.81 (3H, t, CH₂CH₃, J = 6.4 Hz), 1.14 (3H, d, C=OCHCH₃, J = 7.2 Hz), 1.15 – 1.31 (24H, m, C₁₂H₂₄), 1.34 (3H, d, CHCH₃, J = 6.4 Hz), 2.82 (1H, broad s, OH), 3.68 (1H, qd, C=OCHCH₃, J = 7.2, 2.6 Hz),

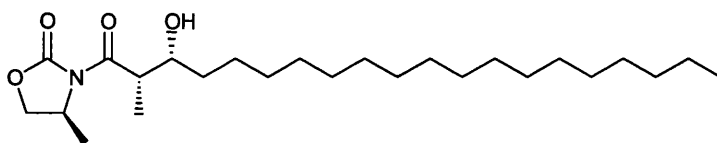
3.85 (1H, broad td, CHOH , $J = 6.4, 1.6$ Hz), 3.94 (1H, dd, $\text{OCH}_\text{A}\text{H}_\text{B}$, $J = 3.0, 8.7$ Hz), 4.38 (1H, apparent t, $\text{OCH}_\text{A}\text{H}_\text{B}$, $J = 8.7$ Hz), 4.52 (1H, m, CHN); ^{13}C NMR (CDCl_3 , 75 MHz): δ 9.7 (CH_3), 13.5 (CH_3), 18.5 (CH_3), 22.1 (CH_2), 25.4 (CH_2), 28.8 (CH_2), 29.0 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 31.3 (CH_2), 33.2 (CH_2), 41.4 (CH), 49.8 (CH), 68.4 (CH_2O), 70.7 (CHOH), 152.2 (OC=O), 176.5 (NC=O); IR (thin film) ν_{max} (cm^{-1}): 3428 (broad OH), 1781 (C=O), 1704 (C=O); HRMS: m/z (ES) $[\text{M}+\text{H}]^+$ requires 370.2952, found 370.2950

(*S*)-3-((2*S*,3*R*)-3-Hydroxy-2-methyl-octadecanoyl)-4-methyl-oxazolidin-2-one, 328



According to general procedure 6.2.12, employing (*S*)-4-methyl-3-propionyloxazolidin-2-one **323** (0.89 g, 5.67 mmol) in DCM (50 mL), 9-BBNOTf (12.5 mL, 0.5 M, 6.24 mmol), diisopropylethylamine (1.3 mL, 7.37 mmol) and hexadecanal **325** (1.50 g, 6.24 mmol) in DCM (5 mL), the crude product was prepared as a dark yellow oil. Purification by column chromatography afforded (*S*)-3-((2*S*,3*R*)-3-hydroxy-2-methyl-octadecanoyl)-4-methyl-oxazolidin-2-one **328** (1.96 g, 87%) as a pale yellow oil.

$[\alpha]_D^{25} + 25.6^\circ$ (c 0.39, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz): δ 0.87 (3H, t, CH_2CH_3 , $J = 6.8$ Hz), 1.21 (3H, d, C=OCHCH_3 , $J = 7.2$ Hz), 1.23 – 1.30 (28H, m, $\text{C}_{14}\text{H}_{28}$), 1.40 (3H, d, NCHCH_3 , $J = 6.4$ Hz), 2.89 (1H, broad s, OH), 3.74 (1H, qd, C=OCHCH_3 , $J = 7.2, 2.6$ Hz), 3.92 (1H, m, CHOH), 4.00 (1H, dd, $\text{OCH}_\text{A}\text{H}_\text{B}$, $J = 3.0, 8.6$ Hz), 4.44 (1H, apparent t, $\text{OCH}_\text{A}\text{H}_\text{B}$, $J = 8.6$ Hz), 4.59 (1H, m, CHN); ^{13}C NMR (CDCl_3 , 75 MHz): δ 10.2 (CH_3), 14.1 (CH_3), 19.1 (CH_3), 22.7 (CH_2), 26.0 (CH_2), 29.3 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 31.9 (CH_2), 33.8 (CH_2), 41.9 (CH), 50.4 (CH), 68.9 (CH_2O), 71.3 (CHOH), 153.0 (OC=O), 177.7 (NC=O); IR (thin film) ν_{max} (cm^{-1}): 3425 (O-H), 1781 (C=O), 1703 (C=O); HRMS: m/z (ES) $[\text{M}+\text{H}]^+$ requires 398.3265, found 398.3266

(S)-3-((2S,3R)-3-Hydroxy-2-methyl-icosanoyl)-4-methyl-oxazolidin-2-one, 329

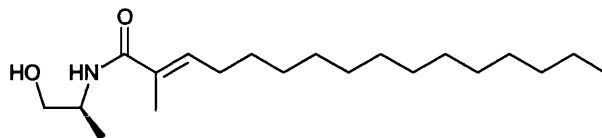
According to general procedure 6.2.12, employing (S)-4-methyl-3-propionyloxazolidin-2-one **323** (0.40 g, 2.55 mmol) in DCM (12 mL), 9-BBNOTf (5.56 mL, 0.5 M, 2.81 mmol), diisopropylethylamine (0.57 mL, 3.32 mmol) and octadecanal **326** (0.75 g, 2.81 mmol) in DCM (5 mL), the crude product was prepared as a yellow oil. Purification by column chromatography afforded (S)-3-((2S,3R)-3-hydroxy-2-methyl-icosanoyl)-4-methyl-oxazolidin-2-one **329** (0.87 g, 80%) as a pale yellow oil.

$[\alpha]_D^{25} + 23.5^\circ$ (c 0.4, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz): δ 0.87 (3H, t, CH_2CH_3 , $J = 6.8$ Hz), 1.21 (3H, d, $\text{C}=\text{OCHCH}_3$, $J = 7.2$ Hz), 1.23 – 1.30 (32H, m, $\text{C}_{16}\text{H}_{32}$), 1.40 (3H, d, NCHCH_3 , $J = 6.4$ Hz), 2.89 (1H, broad s, OH), 3.74 (1H, qd, $\text{C}=\text{OCHCH}_3$, $J = 7.2, 2.6$ Hz), 3.92 (1H, m, CHOH), 4.00 (1H, dd, $\text{OCH}_\text{A}\text{H}_\text{B}$, $J = 3.0, 8.6$ Hz), 4.44 (1H, apparent t, $\text{OCH}_\text{A}\text{H}_\text{B}$, $J = 8.6$ Hz), 4.59 (1H, m, CHN); ^{13}C NMR (CDCl_3 , 75 MHz): δ 10.2 (CH_3), 14.1 (CH_3), 19.1 (CH_3), 22.7 (CH_2), 26.0 (CH_2), 29.3 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 31.9 (CH_2), 33.8 (CH_2), 41.9 (CH), 50.4 (CH), 68.9 (CH_2O), 71.3 (CHOH), 153.0 ($\text{OC}=\text{O}$), 177.7 ($\text{NC}=\text{O}$); IR (thin film) ν_{max} (cm^{-1}): 3412 (O-H), 1788 ($\text{C}=\text{O}$), 1700 ($\text{C}=\text{O}$); HRMS: m/z (ES) $[\text{M}+\text{H}]^+$ requires 426.3578, found 426.3582

6.2.13 Typical procedure for the potassium *tert*-butoxide elimination of *syn*-aldols

4-Methyl-oxazolidin-2-one *syn*-aldol (1 eq.) in THF is cooled to -78°C in an acetone/dry ice bath. Potassium *tert*-butoxide (1 eq.) is added in one portion and the reaction allowed to warm to room temperature over 20 hours. The solvent is removed *in vacuo* and the residue redissolved in DCM, washed with brine, dried (MgSO_4) and the solvent removed *in vacuo* to afford the crude product.

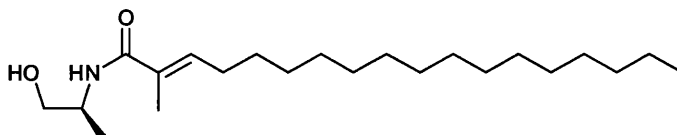
(*E*)-2-Methyl-hexadec-2-enoic acid ((*S*)-2-hydroxy-1-methyl-ethyl)-amide (Semiplenamamide C), 330



According to general procedure 6.2.13, employing (*S*)-3-((2*S*,3*R*)-3-hydroxy-2-methyl-hexadecanoyl)-4-methyl-oxazolidin-2-one **327** (50 mg, 0.14 mmol) in THF (1 mL) and potassium *tert*-butoxide (15 mg, 0.14 mmol) the crude product was prepared as a colourless oil. Purification by column chromatography afforded (*E*)-2-methyl-hexadec-2-enoic acid ((*S*)-2-hydroxy-1-methyl-ethyl)-amide (semiplenamamide C) **330** (34 mg, 74%) as a colourless oil, with spectroscopic data essentially identical to the literature compound.^[205]

$[\alpha]_D^{25}$ - 8.0 ° (c 0.61, CHCl₃) [lit. - 5.0 ° (c 0.30, CHCl₃)]; ¹H NMR (CDCl₃, 300 MHz): δ 0.81 (3H, t, CH₂CH₃, J = 6.6 Hz), 1.14 (3H, apparent d, CHCH₃, J = 7.2 Hz), 1.19 – 1.27 (22H, m, C₁₁H₂₂), 1.78 (1H, broad s, OH), 2.07 (2H, apparent q, J = 7.2 Hz, CH₂CH=C), 3.50 (1H, dd, CH_AH_BOH, J = 6.4, 10.9 Hz), 3.65 (1H, dd, CH_AH_BOH, J = 10.9, 3.4 Hz), 4.07 (1H, m CHCH₃), 5.74 (1H, broad s, NH), 6.32 (1H, apparent dt, CH₂CH=C, J = 7.2, 1.1 Hz); ¹³C NMR (CDCl₃, 75 MHz): δ 10.8 (CH₃), 12.9 (CH₃), 15.9 (CH₃), 21.1 (CH₂), 26.8 (CH₂), 27.1 (CH₂), 27.9 (CH₂), 28.2 (CH₂), 28.5 (CH₂), 28.7 (CH₂), 28.8 (CH₂), 29.3 (CH₂), 31.0 (CH₂), 47.3 (CHN), 66.5 (CH₂OH), 129.1 (C=CH), 136.3 (C=CH), 169.4 (C=O); IR (thin film) ν_{max} (cm⁻¹): 3280 (broad OH), 1621 (C=O); HRMS: m/z (ES) [M+H]⁺ requires 326.3054, found 326.3052

(*E*)-2-Methyl-octadec-2-enoic acid ((*S*)-2-hydroxy-1-methyl-ethyl)-amide, 331

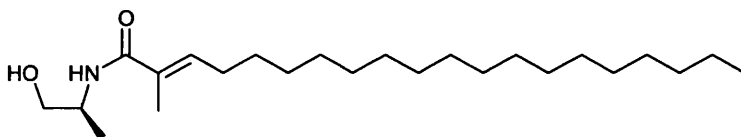


According to general procedure 6.2.13, employing (*S*)-3-((2*S*,3*R*)-3-hydroxy-2-methyl-octadecanoyl)-4-methyl-oxazolidin-2-one **328** (80 mg, 0.20 mmol) in THF (1.5 mL) and

potassium *tert*-butoxide (23 mg, 0.20 mmol) the crude product was prepared. Purification by column chromatography afforded (*E*)-2-methyl-octadec-2-enoic acid ((*S*)-2-hydroxy-1-methyl-ethyl)-amide **331** (56 mg, 79%) as a pale yellow oil.

$[\alpha]_D^{25}$ - 7.2 ° (c 0.5, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 0.88 (3H, t, CH₂CH₃, J = 6.4 Hz), 1.15 (3H, d, CHCH₃, J = 7.2 Hz), 1.25 (24H, m, C₁₂H₂₄), 1.42 (2H, m, CH₂), 2.13 (2H, m, CH₂CH=C), 3.56 (1H, dd, CH_AH_BOH, J = 10.9, 6.4 Hz), 3.71 (1H, dd, CH_AH_BOH, J = 10.9, 3.4 Hz), 4.10 (1H, m, CHCH₃), 5.83 (1H, broad s, NH), 6.38 (1H, dt, C=CH, J = 7.5, 1.5 Hz); ¹³C NMR (CDCl₃, 75 MHz): δ 10.1 (CH₃), 12.5 (CH₃), 14.0 (CH₃), 22.6 (CH₂), 26.8 (CH₂), 28.3 (CH₂), 28.5 (CH₂), 28.7 (CH₂), 28.8 (CH₂), 29.3 (CH₂), 29.6 (CH₂), 31.8 (CH₂), 47.7 (CHN), 71.6 (CH₂OH), 130.2 (C=CH), 137.0 (C=CH), 170.0 (C=O); IR (thin film) ν_{max} (cm⁻¹): 3676 (N-H), 3448 (O-H), 1740 (C=O); HRMS: m/z (ES) [M+H]⁺ requires 354.3368, found 354.3366

(*E*)-2-Methyl-icos-2-enoic acid ((*S*)-2-hydroxy-1-methyl-ethyl)-amide, **332**



According to general procedure 6.2.13, employing (*S*)-3-((2*S*,3*R*)-3-hydroxy-2-methyl-icosanoyl)-4-methyl-oxazolidin-2-one **329** (129 mg, 0.30 mmol) in THF (2 mL) and potassium *tert*-butoxide (34 mg, 0.30 mmol) the crude product was prepared. Purification by column chromatography afforded (*E*)-2-methyl-icos-2-enoic acid ((*S*)-2-hydroxy-1-methyl-ethyl)-amide **332** (85 mg, 74%) as a colourless oil.

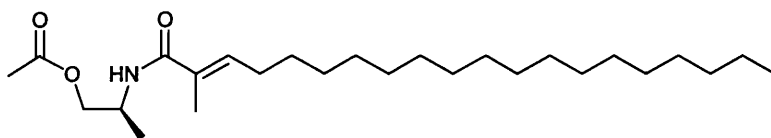
$[\alpha]_D^{25}$ - 7.5 ° (c 0.50, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 0.88 (3H, t, CH₂CH₃, J = 7.0 Hz), 1.21 (3H, apparent d, CH₃CH, J = 7.0 Hz), 1.21 – 1.35 (30H, m, C₁₅H₃₀), 1.42 (1H, broad s, OH), 2.13 (2H, apparent q, CH₂CH=C, J = 7.0 Hz), 3.56 (1H, dd, CH_AH_BOH, J = 11.0, 6.0 Hz), 3.71 (1H, dd, CH_AH_BOH, J = 11.0, 3.5 Hz), 4.12 (1H, apparent qd, CHCH₃, J = 6.5, 3.5 Hz), 5.83 (1H, broad s, NH), 6.37 (1H, apparent td, CH=C, J = 7.5, 1.5 Hz); ¹³C NMR (CDCl₃, 75 MHz): δ 11.7 (CH₃), 13.1 (CH₃), 16.1 (CH₃), 21.7 (CH₂), 27.4 (CH₂), 27.8 (CH₂), 28.3 (CH₂), 28.4 (CH₂), 28.5 (CH₂), 28.6 (CH₂), 28.7 (CH₂), 29.3 (CH₂), 30.9 (CH₂), 47.1 (CHN), 66.7 (CH₂OH), 129.2 (C=CH), 136.1 (C=CH), 169.3

(C=O); IR (thin film) ν_{\max} (cm⁻¹): 3286 (broad OH), 1627 (C=O); HRMS: m/z (ES) [M+H]⁺ requires 382.3680, found 382.3678

6.2.14 Typical procedure for *O*-acylation of 2-hydroxy amides

Unsaturated hydroxy amide (1 eq.) in acetic anhydride and pyridine is stirred for 20 hours before evaporating *in vacuo*. The residue is redissolved in DCM, washed with water and brine, dried (MgSO₄), filtered and the solvent removed *in vacuo* to afford the crude product.

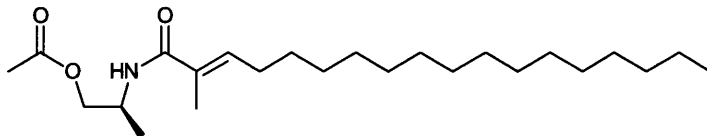
Acetic acid (*S*)-2-((*E*)-2-methyl-icos-2-enoylamino)-propyl ester (Semiplenamide D), 333



According to general procedure 6.2.14, employing (*E*)-2-methyl-icos-2-enoic acid ((*S*)-2-hydroxy-1-methyl-ethyl)-amide **332** (100 mg, 0.26 mmol) in acetic anhydride (1 mL) and approximately 5 drops of pyridine, the crude product is prepared. Purification by column chromatography afforded **acetic acid (*S*)-2-((*E*)-2-methyl-icos-2-enoylamino)-propyl ester (semiplenamide D) 333** (101 mg, 92%) as a colourless oil, with spectroscopic data essentially identical to the literature compound.^[205]

$[\alpha]_D^{25}$ - 10.0 ° (c 0.15, CHCl₃) [lit. - 10.6 ° (c 0.15, CHCl₃)]; ¹H NMR (CDCl₃, 300 MHz): δ 0.89 (3H, t, CH₂CH₃, J = 6.0 Hz), 1.20 (3H, d, CHCH₃, J = 7.0 Hz), 1.25 – 1.29 (28H, broad m, C₁₄H₂₈), 1.41 (2H, m, CH₂CH₂CH), 1.82 (3H, s, CH=CCH₃), 2.08 (3H, s, C=OCH₃), 2.13 (2H, m, CH₂CH=C), 4.05 (1H, dd, CH_AH_BO, J = 5.5, 4.0 Hz), 4.20 (1H, dd, CH_AH_BO, J = 5.5, 5.8 Hz), 4.33 (1H, m, CHN), 5.82 (1H, broad s, NH), 6.33 (1H, tm, CH=C, J = 7.0 Hz); ¹³C NMR (CDCl₃, 75 MHz): δ 13.0 (CH₃), 14.6 (CH₃), 17.5 (CH₃), 20.9 (C=OCH₃), 23.0 (CH₂), 23.1 (CH₂), 28.7 (CH₂), 29.0 (CH₂), 30.5 (CH₂), 32.2 (CH₂), 45.2 (CHNH), 67.7 (CH₂O), 131.8 (C=CH), 137.0 (C=CH), 169.3 (NC=O), 171.8 (OC=O); IR (thin film) ν_{\max} (cm⁻¹): 3279 (N-H), 1721 (C=O), 1655 (C=O); HRMS: m/z (ES) [M+H]⁺ requires 424.3712, found 424.3710

Acetic acid (*S*)-2-((*E*)-2-methyl-octadec-2-enoylamino)-propyl ester (Semiplenamamide E), 334



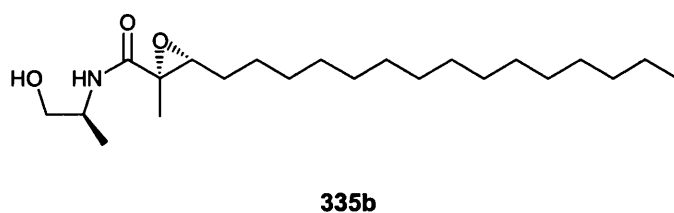
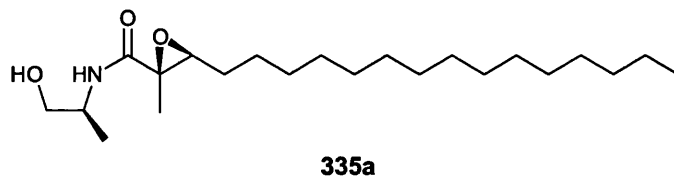
According to general procedure 6.2.14, employing (*E*)-2-methyl-octadec-2-enoic acid ((*S*)-2-hydroxy-1-methyl-ethyl)-amide **331** (107 mg, 0.30 mmol) in acetic anhydride (1.5 mL) and approximately 5 drops of pyridine, the crude product is prepared. Purification by column chromatography afforded **acetic acid (*S*)-2-((*E*)-2-methyl-octadec-2-enoylamino)-propyl ester (semiplenamamide E) 334** (112 mg, 94%) as a colourless oil, with spectroscopic data essentially identical to the literature compound.^[205]

$[\alpha]_D^{25}$ - 26.7 ° (c 0.15, CHCl₃) [lit. - 7.1 ° (c 0.28, CHCl₃)]; ¹H NMR (CDCl₃, 300 MHz): δ 0.87 (3H, t, CH₂CH₃, J = 6.0 Hz), 1.19 (3H, d, CHCH₃, J = 7.0 Hz), 1.22 – 1.29 (24H, broad m, C₁₂H₂₄), 1.40 (2H, m, CH₂CH₂CH), 1.81 (3H, s, CH=CCH₃), 2.07 (3H, s, C=OCH₃), 2.12 (2H, m, CH₂CH=C), 4.02 (1H, dd, CH_AH_BO, J = 5.5, 4.0 Hz), 4.18 (1H, dd, CH_AH_BO, J = 5.5, 5.8 Hz), 4.33 (1H, m, CHN), 5.85 (1H, broad s, NH), 6.32 (1H, tm, CH=C, J = 7.0 Hz); ¹³C NMR (CDCl₃, 75 MHz): δ 13.0 (CH₃), 14.5 (CH₃), 17.8 (CH₃), 21.3 (C=OCH₃), 23.0 (CH₂), 28.8 (CH₂), 29.5 (CH₂), 29.7 (CH₂), 29.9 (CH₂), 30.1 (CH₂), 32.3 (CH₂), 45.1 (CHNH), 67.4 (CH₂O), 130.8 (C=CH), 137.1 (C=CH), 169.3 (NC=O), 171.8 (OC=O); IR (thin film) ν_{max} (cm⁻¹): 3676 (N-H), 1735 (C=O), 1660 (C=O); HRMS: m/z (ES) [M+H]⁺ requires 396.3472, found 396.3470

6.2.15 Typical procedure for the epoxidation of unsaturated amides

3-Chloroperoxybenzoic acid (11.6 eq.) was added to the desired unsaturated amide (1 eq.) in DCM and left to stir at room temperature for 20 hours. The reaction mixture is washed with 5% NaOH and water, dried (MgSO₄), filtered and evaporated *in vacuo* to yield the crude product.

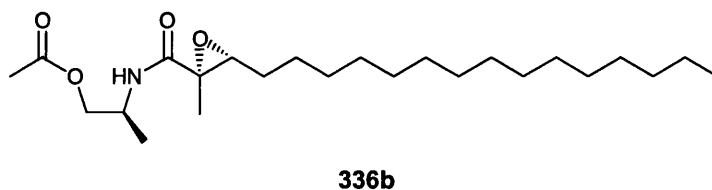
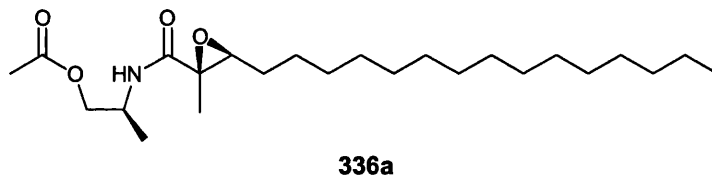
2-Methyl-3-pentadecyl-oxirane-2-carboxylic acid ((*S*)-2-hydroxy-1-methyl-ethyl)-amide **335a (Semiplenamamide F) and **335b****



According to general procedure 6.2.15, employing (*E*)-2-methyl-octadec-2-enoic acid ((*S*)-2-hydroxy-1-methyl-ethyl)-amide **331** (10 mg, 0.028 mmol) in DCM (5 mL) and 3-chloroperoxybenzoic acid (57 mg, 0.328 mmol), the crude product was prepared as a colourless oil. Purification by column chromatography afforded a 45:55 mixture of diastereomers **335a** and **335b** (9.3 mg, 90%) as a cloudy oil.

$[\alpha]_D^{25} + 0.3^\circ$ (c 0.20, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz): δ 0.88 (6H, t, **335a** CH_2CH_3 and **335b** CH_2CH_3 , $J = 6.4$ Hz), 1.16 (3H, d, **335a** CHCH_3 , $J = 7.2$ Hz), 1.18 (3H, d, **335b** CHCH_3 , $J = 6.8$ Hz), 1.25 – 1.32 (48H, m, **335a** $\text{C}_{12}\text{H}_{24}$ and **335b** $\text{C}_{12}\text{H}_{24}$), 1.43 (4H, overlapping m, **335a** CH_2CH_3 and **335b** CH_2CH_3), 1.55 (6H, s, **335a** CH_3CO and **335b** CH_3CO), 1.57 (4H, overlapping m, **335a** CH_2CHO and **335b** CH_2CHO), 2.86 (1H, t, **335b** CH_2CHO , $J = 5.6$ Hz), 2.89 (1H, t, **335a** CH_2CHO , $J = 6.2$ Hz), 3.52 (2H, apparent d, **335b** CH_2O , $J = 5.3$ Hz), 3.68 (2H, dd, **335a** CH_2O , $J = 4.9, 1.1$ Hz), 4.03 (2H, m, **335a** CHNH and **335b** CHNH), 6.40 (1H, broad s, NH), 6.45 (1H, broad s, NH); ^{13}C NMR (CDCl_3 , 75 MHz): δ 12.8 (CH_3), 14.1 (CH_3), 17.3 (CH_3), 23.7 (CH_2), 26.6 (CH_2), 28.3 (CH_2), 29.6 (CH_2), 30.0 (CH_2), 31.0 (CH_2), 31.9 (CH_2), 47.5 (CHN), 60.1 (CH_3CO), 63.8 (CH_2CHO), 67.7 (CH_2O), 173.3 (C=O) all peaks exhibit a corresponding peak for **335b**; IR (thin film) ν_{max} (cm^{-1}): 3296 (broad OH), 1646 (C=O); HRMS: m/z (ES) $[\text{M}+\text{H}]^+$ requires 370.3808, found 370.3803

Acetic acid (*S*)-2-[(2-methyl-3-pentadecyl-oxiranecarbonyl)-amino]-propyl ester **336a (Semiplenamide G) and **336b****

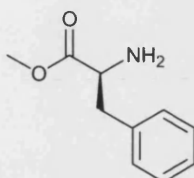


According to general procedure 6.2.15, employing acetic acid (*S*)-2-((*E*)-2-methyl-octadec-2-enoylamino)-propyl ester (semiplenamide E) **334** (10 mg, 0.025 mmol) in DCM (5 mL) and 3-chloroperoxybenzoic acid (50 mg, 0.29 mmol) the crude product was prepared. Purification by column chromatography afforded a 45:55 mixture of **336a** and **336b** (10 mg, 95%) as a cloudy oil.

$[\alpha]_D^{25} + 0.5^\circ$ (c 0.20, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 0.87 (6H, t, **336a** CH₂CH₃ and **336b** CH₂CH₃, J = 6.4 Hz), 1.12 (3H, d, **336a** CHCH₃, J = 7.2 Hz), 1.17 (3H, d, **336b** CHCH₃, J = 6.8 Hz), 1.23 – 1.32 (48H, m, **336a** C₁₂H₂₄ and **336b** C₁₂H₂₄), 1.46 (4H, overlapping m, **336a** CH₂CH₃ and **336b** CH₂CH₃), 1.50 (6H, s, **336a** CH₃CO and **336b** CH₃CO), 1.55 (4H, overlapping m, **336a** CH₂CHO and **336b** CH₂CHO), 2.06 (3H, s, **336b** C=OCH₃), 2.08 (3H, s, **336a** C=OCH₃), 2.81 (1H, t, **336b** CH₂CHO, J = 5.6 Hz), 2.83 (1H, t, **336a** CH₂CHO, J = 6.2 Hz), 3.99 (2H, apparent d, **336b** CH₂O, J = 5.3 Hz), 4.03 (2H, dd, **336a** CH₂O, J = 4.9, 1.1 Hz), 4.20 (2H, m, **336a** CHNH and **336b** CHNH), 6.37 (1H, broad s, NH), 6.42 (1H, broad s, NH); ¹³C NMR (CDCl₃, 75 MHz): δ 12.9 (CH₃), 14.1 (CH₃), 17.2 (CH₃), 20.8 (C=OCH₃), 22.7 (CH₂), 26.2 (CH₂), 28.1 (CH₂), 29.3 (CH₂), 29.6 (CH₂), 31.0 (CH₂), 31.9 (CH₂), 43.6 (CHN), 60.0 (CH₃CO), 63.8 (CH₂CHO), 66.7 (CH₂O), 171.2 (C=O), 173.3 (C=O) all peaks exhibit a corresponding peak for **336b**; IR (thin film) ν_{\max} (cm⁻¹): 3283 (O-H), 1723 (C=O), 1655 (C=O); HRMS: m/z (ES) [M+H]⁺ requires 412.3428, found 412.3427

6.2.16 Procedures for the synthesis of (*S*)-4-benzyl-5,5-dimethyl-oxazolidin-2-one (SuperQuat auxiliary), 344

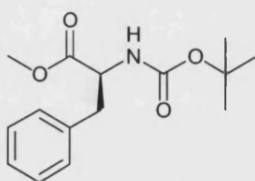
(*S*)-Phenylalanine methyl ester, 347



Thionyl chloride (33.1 mL, 0.45 mol) was added dropwise to a stirred suspension of (L)-phenylalanine (50 g, 0.30 mol) in methanol (500 mL) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 30 hrs. The solvent was removed *in vacuo* to give (*S*)-phenylalanine methyl ester **347** (58 g, 90%) with ¹H NMR spectroscopic data essentially identical to the literature compound.^[234] The crude product was used in the next step without further purification.

¹H NMR (CDCl₃, 300 MHz): δ 2.87 (1H, dd, CH_AH_BPh, J = 13.5, 5.0 Hz), 3.07 (1H, dd, CH_AH_BPh, J = 13.5, 5.0 Hz) 3.71 (3H, s, CH₃O), 3.75 (1H, dd, CHN, J = 8.0, 5.0 Hz), 7.24 – 7.35 (5H, broad m, Ph)

(*S*)-*N*-Boc-phenylalanine methyl ester, 348



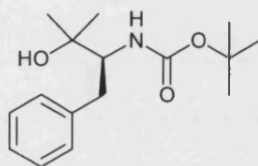
To a stirred solution of (*S*)-phenylalanine methyl ester **347** (65.4 g, 0.30 mol) in ethanol (500 mL) at 0 °C was added NaHCO₃ (76.42 g, 0.90 mol) and Boc anhydride (69.50 g, 0.32 mol). The reaction was allowed to warm to room temperature and stirred for 48 hrs. The mixture was filtered through Celite, washed with diethyl ether and the filtrate evaporated *in vacuo*. The residue was redissolved in diethyl ether, filtered through Celite and evaporated *in vacuo* to yield (*S*)-*N*-Boc-phenylalanine methyl ester **348** (69.6 g,

83%) with ^1H NMR spectroscopic data essentially identical to the literature compound.^[234]

The crude product was used in the next step without further purification.

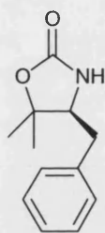
^1H NMR (CDCl_3 , 300 MHz): δ 1.34 (9H, s, *t*-Bu), 3.01 (2H, m, CH_2Ph), 3.64 (3H, s, CH_3O), 4.53 (1H, m, CHNH), 4.89 (1H, m, NH), 7.00 – 7.07 (2H, m, Ph), 7.14 – 7.25 (3H, broad m, Ph)

***tert*-Butyl-(*S*)-3-hydroxy-3-methyl-1-phenylbutan-2-ylcarbamate, 349**



Methyl iodide (1 mL) was added dropwise to a suspension of magnesium turnings (3.48 g, 0.14 mol) in diethyl ether (40 mL), until the reaction sustained a gentle reflux. Methyl iodide (8.91 mL, 0.14 mol) in ether (65 mL) was added dropwise over a period of 30 minutes. The solution was allowed to cool to room temperature, before (*S*)-*N*-Boc-phenylalanine methyl ester **348** (10 g, 0.036 mol) in ether (40 mL) was added dropwise to the reaction over a period of 30 minutes. The reaction was stirred for 48 hours, quenched with saturated ammonium chloride solution and hydrochloric acid (20 mL, 1 M solution in water), filtered through Celite and washed with ether. The solvent was removed under reduced pressure, dissolved in ether, washed with brine and dried (MgSO_4). The solvent was removed *in vacuo* to give ***tert*-butyl-(*S*)-3-hydroxy-3-methyl-1-phenylbutan-2-ylcarbamate 349** as an off white solid which was used in the next step without further purification.

mp 101 – 103 °C; $[\alpha]_D^{25}$ - 44.8 ° (c 1.00, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz): δ 1.20 (9H, s, *t*-Bu), 1.22 (6H, s, $(\text{CH}_3)_2$), 2.51 (1H, m, $\text{CH}_A\text{H}_B\text{Ph}$), 3.02 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, $J = 14.0$, 3.5 Hz), 3.61 (1H, m, CHN), 4.47 (1H, d, NH , $J = 9.0$ Hz), 7.08 – 7.25 (5H, m, Ph); ^{13}C NMR (CDCl_3 , 75 MHz): δ 26.8 (CH_3), 27.5 (CH_3), 28.4 (CH_3), 36.3 (CH_2Ph), 60.7 (CHNH), 73.4 (C), 79.5 (C), 126.4 (phenyl CH), 128.6 (phenyl CH), 129.3 (phenyl CH), 139.3 (phenyl C), 156.8 (C=O); IR (KBr disc) ν_{max} (cm^{-1}): 3475 (O-H), 3379 (N-H), 1662 (C=O); HRMS: m/z (ES) $[\text{M}+\text{H}]^+$ requires 280.1907, found 280.1911.

(S)-4-Benzyl-5,5-dimethyl-oxazolidin-2-one (SuperQuat auxiliary), 344

To a stirred solution of *tert*-butyl-(*S*)-3-hydroxy-3-methyl-1-phenylbutan-2-ylcarbamate **349** (4.0 g, 14.32 mmol) in THF (70 mL) at 0 °C was added potassium *tert*-butoxide (1.6 g, 15.75 mmol) in one portion. After 30 minutes the solvent is evaporated *in vacuo* and the residue dissolved in ethyl acetate, washed with brine, dried (MgSO₄) and evaporated *in vacuo* to afford the crude product. Recrystallisation (ether, petrol) afforded (*S*)-4-benzyl-5,5-dimethyl-oxazolidin-2-one (SuperQuat auxiliary) **344** (3.55 g, 95%) as a white solid with spectroscopic data essentially identical to the literature compound.^[207]

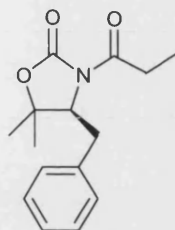
mp 64 – 65 °C [lit. 59 °C]; $[\alpha]_D^{25}$ - 119.5 ° (c 0.80, CHCl₃) [lit. - 103.5 ° (c 0.60, CHCl₃)]; ¹H NMR (CDCl₃, 300 MHz): δ 1.33 (6H, s, C(CH₃)₂), 2.59 (1H, dd, CH_AH_BPh, J = 4.3, 13.6 Hz), 2.72 (1H, dd, CH_AH_BPh, J = 13.6, 10.2 Hz), 3.59 (1H, apparent dd, CHN, J = 10.2, 3.8 Hz), 5.35 (1H, broad s, NH), 7.07 - 7.33 (5H, m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 22.3 (CH₃), 28.0 (CH₃), 37.5 (CH₂Ph), 63.4 (CHN), 83.5 (C(CH₃)₂), 127.6 (phenyl CH), 129.3 (phenyl CH), 129.5 (phenyl CH), 137.3 (phenyl C), 158.2 (C=O); IR (KBr disc) ν_{max} (cm⁻¹): 3379 (N-H), 3475 (O-H), 1662 (C=O)

6.2.17 Typical procedure for the N-acylation of (S)-4-benzyl-5,5-dimethyl-oxazolidin-2-one (SuperQuat auxiliary) 344

(*S*)-4-Benzyl-5,5-dimethyl-oxazolidin-2-one **344** (1 eq.) in dry THF was cooled to - 78 °C before addition of butyl lithium (1.01 eq., 2.5 M solution in hexanes) slowly over a 10 minute period followed by the acid chloride (1.1 eq.). The mixture was left stirring at - 78 °C for 45 min before warming to room temperature whilst stirring for 1 hour and excess acid chloride quenched by addition of aqueous ammonium chloride. Most of the THF and hexane was removed by evaporation *in vacuo* and the organics extracted with DCM. The

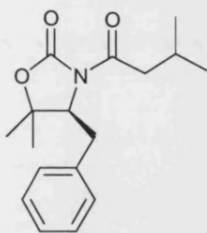
combined organic extracts were washed with 1 M NaOH and brine, dried (MgSO₄), filtered and evaporated *in vacuo*.

(S)-4-Benzyl-5,5-dimethyl-3-propionyl-oxazolidin-2-one, 346



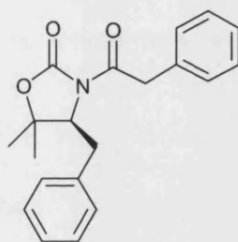
According to general procedure 6.2.17, employing (S)-4-benzyl-5,5-dimethyl-oxazolidin-2-one **344** (1.0 g, 4.87 mmol) in THF (15 mL), butyl lithium (1.97 mL, 2.5 M solution, 4.92 mmol) and propionyl chloride (0.59 mL, 5.36 mmol) the crude product was prepared as a colourless oil. Purification by column chromatography afforded **(S)-4-benzyl-5,5-dimethyl-3-propionyl-oxazolidin-2-one 346** (1.08 g, 85%) as a white solid.

mp 60 – 62 °C; $[\alpha]_D^{25}$ - 30.0 ° (c 0.87, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 1.18 (3H, t, CH₃, J = 7.5 Hz), 1.33 (3H, s, C(CH₃)₂), 1.35 (3H, s, C(CH₃)₂), 2.89 (3H, overlapping m, CH₂CH₃ and CH_AH_BPh), 3.12 (1H, dd, CH_AH_BPh, J = 14.5, 4.0 Hz), 4.50 (1H, dd, CHN, J = 9.5, 4.0 Hz), 7.18 – 7.32 (5H, m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 9.0 (CH₃), 22.7 (C(CH₃)₂), 29.1 (C(CH₃)₂), 29.8 (CH₂), 35.8 (CH₂Ph), 63.9 (CHN), 82.6 (C(CH₃)₂), 127.2 (phenyl CH), 129.1 (phenyl CH), 129.4 (phenyl CH), 137.2 (phenyl C), 152.9 (OC=O), 173.9 (NC=O); IR (KBr disc) ν_{max} (cm⁻¹): 1770 (C=O), 1700 (C=O); HRMS : m/z (ES) [M+H]⁺ requires 262.1438, found 262.1442.

(S)-4-Benzyl-5,5-dimethyl-3-(3-methyl-butyryl)-oxazolidin-2-one, 355

According to general procedure 6.2.17, employing (*S*)-4-benzyl-5,5-dimethyl-oxazolidin-2-one **344** (1.0 g, 4.87 mmol) in THF (15 mL), butyl lithium (1.97 mL, 2.5 M solution, 4.92 mmol) and isovaleryl chloride (0.65 mL, 5.36 mmol) the crude product was prepared as a colourless oil. Purification by column chromatography afforded (*S*)-4-benzyl-5,5-dimethyl-3-(3-methyl-butyryl)-oxazolidin-2-one **355** (1.11 g, 79%) as a colourless oil.

$[\alpha]_D^{25}$ - 33.9 ° (c 0.60, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 0.95 (6H, apparent d, CH(CH₃)₂, J = 7.2 Hz), 1.33 (3H, s, C(CH₃)₂), 1.34 (3H, s, C(CH₃)₂), 2.13 (1H, m, CH(CH₃)₂), 2.78 (2H, apparent d, CH₂-ⁱPr, J = 6.5 Hz), 2.86 (1H, apparent dd, CH_AH_BPh, J = 14.5, 9.6 Hz) 3.11 (1H, dd, CH_AH_BPh, J = 14.5, 4.0 Hz), 4.50 (1H, dd, CHN, J = 9.6, 4.0 Hz), 7.18 – 7.31 (5H, m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 22.6 (CH₃), 22.9 (CH₃), 25.6 (CH(CH₃)₂), 28.8 (C(CH₃)₂), 35.8 (CH₂Ph), 44.5 (CH₂-ⁱPr), 63.9 (CHN), 82.5 (C(CH₃)₂), 127.2 (phenyl CH), 129.2 (phenyl CH), 129.5 (phenyl CH), 137.3 (phenyl C), 152.9 (OC=O), 173.0 (NC=O); IR (thin film) ν_{max} (cm⁻¹): 1779 (C=O), 1699 (C=O); HRMS m/z (ES) [M+H]⁺ requires 290.1751, found 290.1749

(S)-4-Benzyl-5,5-dimethyl-3-phenylacetyl-oxazolidin-2-one, 356

According to general procedure 6.2.17, employing (*S*)-4-benzyl-5,5-dimethyl-oxazolidin-2-one **344** (1.0 g, 4.87 mmol) in THF (15 mL), butyl lithium (1.97 mL, 2.5 M solution, 4.92 mmol) and phenyl acetyl chloride (0.71 mL, 5.36 mmol) the crude product was prepared as a colourless oil. Purification by column chromatography afforded (*S*)-4-benzyl-5,5-dimethyl-3-phenylacetyl-oxazolidin-2-one **356** (1.23 g, 78%) as a colourless oil.

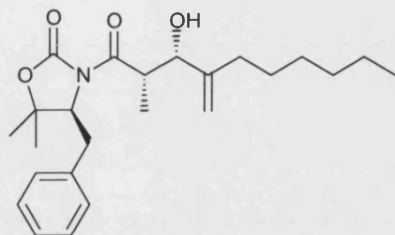
$[\alpha]_D^{25}$ - 15.8 ° (c 0.50, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 1.33 (3H, s, C(CH₃)₂), 1.35 (3H, s, C(CH₃)₂), 2.87 (1H, dd, CH_AH_BPh, J = 14.5, 4.0 Hz), 3.12 (1H, dd, CH_AH_BPh, J = 14.5, 10.0 Hz), 4.28 (2H, apparent s, C=OCH₂), 4.51 (1H, dd, CHN, J = 10.0, 4.0 Hz), 7.17 – 7.38 (10H, m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 22.6 (C(CH₃)₂), 28.6 (C(CH₃)₂), 36.0 (CH₂), 42.3 (CH₂), 64.2 (CHN), 82.9 (C(CH₃)₂), 127.2 (phenyl CH), 127.6 (phenyl CH), 129.0 (phenyl CH), 129.1 (phenyl CH), 129.6 (phenyl CH), 130.1 (phenyl CH), 134.1 (phenyl C), 137.2 (phenyl C), 153.3 (OC=O), 172.0 (NC=O); IR (thin film) ν_{max} (cm⁻¹): 1777 (C=O), 1697 (C=O); HRMS m/z (ES) [M+H]⁺ requires 324.1594, found 324.1594

6.2.18 Typical procedure for the SuperQuat mediated *syn*-aldol reaction

A solution of *N*-acylated oxazolidinone (1 eq.) in DCM is cooled to 0 °C in an ice bath and 9-BBNOTf (1.1 eq., 0.5 M solution in hexanes) added dropwise. The mixture is left stirring for 30 min at 0 °C before addition of diisopropylethylamine (1.3 eq.) and stirring for a further 40 min. The reaction is then cooled to - 78 °C in an acetone-dry ice bath before addition of the aldehyde (1.1 eq.) and stirring for 1 hr at - 78 °C followed by 1 hr at 0 °C. The mixture is allowed to warm to room temperature, pH 7 phosphate buffer added and stirred for 5 min before addition of 2:1 hydrogen peroxide:methanol (v/v) and stirring for 16 hrs. The bulk of the solvent is removed *in vacuo* and the resulting slurry partitioned

between water and diethyl ether. The combined organic extracts are washed with 5 % Na_2CO_3 and brine, dried (MgSO_4), filtered and evaporated *in vacuo*.

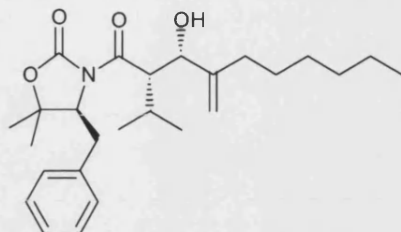
(*S*)-4-Benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylene-decanoyl)-5,5-dimethyl-oxazolidin-2-one, 350



According to general procedure 6.2.18, employing (*S*)-4-benzyl-5,5-dimethyl-3-propionyl-oxazolidin-2-one **346** (2.5 g, 9.57 mmol) in DCM (100 mL), 9-BBNOTf (21.05 mL, 0.5 M, 10.52 mmol), diisopropylethylamine (2.17 mL, 12.44 mmol) and 2-methylene-octanal **283** (1.48 g, 10.52 mmol) the crude product was prepared as a pale yellow oil. Purification by column chromatography afforded (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylene-decanoyl)-5,5-dimethyl-oxazolidin-2-one **350** (3.20 g, 83%) as a colourless oil.

$[\alpha]_D^{25}$ - 27.8 ° (c 1.15, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz): δ 0.87 (3H, t, CH_2CH_3 , J = 6.8 Hz), 1.11 (3H, d, CHCH_3 , J = 7.2 Hz), 1.28 (6H, m, CH_2), 1.37 (3H, s, $\text{C}(\text{CH}_3)_2$), 1.39 (3H, s, $\text{C}(\text{CH}_3)_2$), 1.45 (2H, m, CH_2), 1.98 (2H, m, $\text{CH}_2\text{C}=\text{C}$), 2.76 (1H, broad s, OH), 2.90 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, J = 14.3, 9.0 Hz), 3.08 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, J = 14.3, 4.5 Hz), 3.95 (1H, qd, CHCH_3 , J = 7.2, 3.4 Hz), 4.38 (1H, d, CHOH , J = 3.4 Hz), 4.53 (1H, dd, CHN , J = 9.0, 4.5 Hz), 4.96 (1H, m, $\text{C}=\text{CH}_A\text{H}_B$), 5.15 (1H, apparent s, $\text{C}=\text{CH}_A\text{H}_B$), 7.19 - 7.33 (5H, m, Ph); ^{13}C NMR (CDCl_3 , 75 MHz): δ 10.6 (CH_3), 14.1 (CH_3), 22.2 ($\text{C}(\text{CH}_3)_2$), 22.6 (CH_2), 27.8 (CH_2), 28.4 ($\text{C}(\text{CH}_3)_2$), 29.1 (CH_2), 31.7 (CH_2), 32.6 (CH_2), 35.3 (CH_2Ph), 40.5 (CHCH_3), 63.4 (CHN), 73.3 (CHOH), 82.3 ($\text{C}(\text{CH}_3)_2$), 110.4 ($\text{C}=\text{CH}_2$), 126.9 (phenyl CH), 128.6 (phenyl CH), 129.1 (phenyl CH), 136.6 (phenyl C), 148.3 (C), 152.2 (C), 177.3 ($\text{NC}=\text{O}$); IR (thin film) ν_{max} (cm^{-1}): 3499 (O-H), 1780 ($\text{C}=\text{O}$), 1700 ($\text{C}=\text{O}$); HRMS m/z (ES) $[\text{M}+\text{H}]^+$ requires 402.2639, found 402.2637

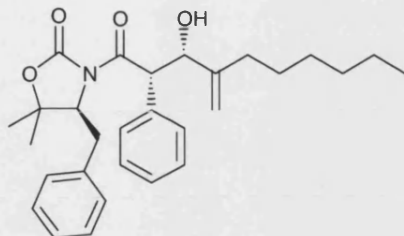
(*S*)-4-Benzyl-3-((2*S*,3*S*)-3-hydroxy-2-isopropyl-4-methylene-decanoyl)-5,5-dimethyl-oxazolidin-2-one, 357



According to general procedure 6.2.18, employing (*S*)-4-benzyl-5,5-dimethyl-3-(3-methylbutyryl)-oxazolidin-2-one **355** (0.30 g, 1.02 mmol) in DCM (15 mL), 9-BBNOTf (2.24 mL, 0.5 M, 1.12 mmol), diisopropylethylamine (0.23 mL, 1.33 mmol) and 2-methylene-octanal **283** (0.16 g, 1.12 mmol) the crude product was prepared as a pale yellow oil. Purification by column chromatography afforded (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-isopropyl-4-methylene-decanoyl)-5,5-dimethyl-oxazolidin-2-one **357** (0.35 g, 79%) as a pale yellow oil.

$[\alpha]_D^{25}$ - 25.9 ° (c 1.16, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 0.85 (3H, m, CH₂CH₃), 0.99 (3H, d, CH(CH₃)₂, J = 6.8 Hz), 1.02 (3H, d, CH(CH₃)₂, J = 7.2 Hz), 1.27 (H₁₂, m, C₃H₆ and C(CH₃)₂), 1.41 (2H, m, CH₂), 1.91 (1H, d, OH, J = 4.9 Hz), 2.06 (2H, m, CH₂C=C), 2.30 (1H, m, CH(CH₃)₂), 2.82 (1H, dd, CH_AH_BPh, J = 14.3, 10.2 Hz), 3.11 (1H, dd, CH_AH_BPh, J = 14.3, 3.6 Hz), 4.32 (1H, dd, CH-ⁱPr, J = 8.7, 4.8 Hz), 4.39 (1H, dd, CHOH, J = 8.8, 4.8 Hz), 4.48 (1H, dd, CHN, J = 10.2, 3.8 Hz), 4.85 (1H, m, C=CH_AH_B), 5.08 (1H, apparent s, C=CH_AH_B), 7.16 – 7.31 (5H, m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 14.1 (CH₃), 18.6, 20.8, 22.2, 22.6 (CH₂), 27.8 (CH₂), 28.1, 28.3, 29.1 (CH₂), 31.7 (CH₂), 32.6 (CH₂), 35.5 (CH₂Ph), 50.7 (CH-ⁱPr), 63.6 (CHN), 74.4 (CHOH), 81.7 (C(CH₃)₂), 111.2 (C=CH₂), 126.8 (phenyl CH), 128.6 (phenyl CH), 129.0 (phenyl CH), 136.9 (phenyl C), 151.0 (C), 152.5 (C), 173.8 (NC=O); IR (thin film) ν_{max} (cm⁻¹): 3494 (O-H), 1777 (C=O), 1691 (C=O); HRMS: m/z (ES) [M+H]⁺ requires 430.2952, found 430.2956

(*S*)-4-Benzyl-3-((2*S*,3*S*)-3-hydroxy-4-methylene-2-phenyl-decanoyl)-5,5-dimethyl-oxazolidin-2-one, 358



According to general procedure 6.2.18, employing (*S*)-4-benzyl-5,5-dimethyl-3-phenylacetyl-oxazolidin-2-one **356** (0.35 g, 1.08 mmol) in DCM (15 mL), 9-BBNOTf (2.38 mL, 0.5 M, 1.19 mmol), diisopropylethylamine (0.25 mL, 1.40 mmol) and 2-methylene-octanal **283** (0.17 g, 1.19 mmol) the crude product was prepared as a yellow oil. Purification by column chromatography afforded (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-4-methylene-2-phenyl-decanoyl)-5,5-dimethyl-oxazolidin-2-one **358** (0.35 g, 70%) as a pale yellow oil.

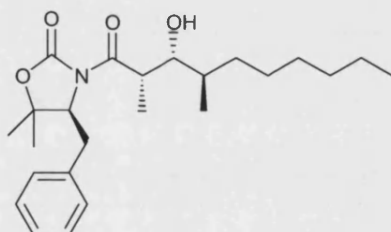
$[\alpha]_D^{25}$ - 56.2 ° (c 1.05, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 0.87 (3H, t, CH₂CH₃, J = 6.8 Hz), 1.25 - 1.37 (6H, broad m, C₃H₆), 1.30 (3H, s, C(CH₃)₂), 1.34 (3H, s, C(CH₃)₂), 1.53 (2H, m, CH₂), 2.12 (2H, m, CH₂), 2.14 (1H, d, OH, J = 3.4 Hz), 2.69 (1H, dd, CH_AH_BPh, J = 14.7, 9.2 Hz), 2.89 (1H, dd, CH_AH_BPh, J = 14.7, 4.1 Hz), 4.49 (1H, dd, CHN, J = 9.0, 4.1 Hz), 4.74 (1H, dd, CHOH, J = 7.9, 3.0 Hz), 4.91 (1H, m, C=CH_AH_B), 5.04 (1H, apparent s, C=CH_AH_B), 5.34 (1H, d, CHPh, J = 7.9 Hz), 7.08 – 7.19 (5H, m, Ph), 7.30 – 7.38 (3H, m, Ph), 7.42 – 7.47 (2H, m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 14.1 (CH₃), 22.1 (CH₃), 22.6 (CH₂), 27.8 (CH₂), 28.3 (CH₃), 29.2 (CH₂), 31.7 (CH₂), 32.4 (CH₂), 34.9 (CH₂Ph), 53.2 (CHPh), 63.2 (CHN), 75.9 (CHOH), 82.1 (C(CH₃)₂), 111.9 (C=CH₂), 126.7 (phenyl CH), 127.9 (phenyl CH), 128.6 (phenyl CH), 128.6 (phenyl CH), 128.9 (phenyl CH), 129.8 (phenyl CH), 134.3 (phenyl C), 136.5 (phenyl C), 149.1 (C=CH₂), 152.0 (OC=O), 172.5 (NC=O); IR (thin film) ν_{max} (cm⁻¹): 3511 (O-H), 1777 (C=O), 1692 (C=O); HRMS m/z (ES) [M+Na]⁺ requires 486.2615, found 486.2611

6.2.19 Typical procedure for the hydrogenation of SuperQuat aldols

A: Using the Endeavour catalyst screening system, unsaturated aldol (1 eq.) was dissolved in DCM in a dry reaction tube and placed in the hydrogenator at 25 °C. The sealed vessel was purged three times with nitrogen before injection of the hydrogenation catalyst in DCM and pressurising with hydrogen to the required pressure. After 24 hours the crude mixture was removed from the hydrogenator and filtered through a plug of silica, washed with methyl *tert*-butyl ether and evaporated *in vacuo*.

B: Using the Parr pressure vessel, unsaturated aldol (1 eq.) was dissolved in DCM and added to the vessel under a nitrogen atmosphere at room temperature. The hydrogenation catalyst in DCM was added under nitrogen before sealing of the vessel and pressurising with hydrogen to the desired pressure. After 24 hours the crude mixture was filtered through a plug of silica, washed with diethyl ether and evaporated *in vacuo*.

(*S*)-4-Benzyl-3-((2*S*,3*R*,4*R*)-3-hydroxy-2,4-dimethyl-decanoyl)-5,5-dimethyl-oxazolidin-2-one, (4*R*)-351a

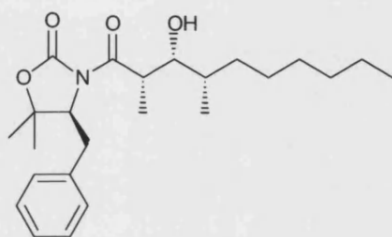


According to general procedure 6.2.19 B, employing (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylene-decanoyl)-5,5-dimethyl-oxazolidin-2-one **350** (50 mg, 0.125 mmol) in DCM (0.5 mL) the crude product was prepared as a pale yellow oil. Purification by column chromatography afforded **(*S*)-4-benzyl-3-((2*S*,3*R*,4*R*)-3-hydroxy-2,4-dimethyl-decanoyl)-5,5-dimethyl-oxazolidin-2-one (4*R*)-351a** as an off white solid.

mp 84 – 86 °C; $[\alpha]_D^{25}$ - 19.2 ° (c 1.30, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 0.87 (6H, m, CH₂CH₃ and CHCH₃), 1.15 (3H, d, C=OCHCH₃, J = 7.2 Hz), 1.27 (8H, m, C₄H₈), 1.38 (3H, s, C(CH₃)₂), 1.40 (3H, s, C(CH₃)₂), 1.55 (2H, m, CH₂), 1.71 (1H, m, CHCH₃), 2.83 (1H, broad s, OH), 2.90 (1H, dd, CH_AH_BPh, J = 14.3, 9.0 Hz), 3.06 (1H, dd, CH_AH_BPh, J = 14.3, 4.5 Hz), 3.56 (1H, dd, CHOH, J = 8.7, 2.6 Hz), 3.92 (1H, qd, C=OCHCH₃, J = 7.2,

2.6 Hz), 4.54 (1H, dd, CHN, $J = 9.0, 4.5$ Hz), 7.19 – 7.34 (5H, m, Ph); ^{13}C NMR (CDCl_3 , 75 MHz): δ 10.1 (CH_3), 14.1 (CH_3), 15.3 (CH_3), 22.2 ($\text{C}(\text{CH}_3)_2$), 22.6 (CH_2), 26.7 (CH_2), 28.4 ($\text{C}(\text{CH}_3)_2$), 29.7 (CH_2), 31.9 (CH_2), 32.5 (CH_2), 35.4 (CH_2Ph), 35.6 (CHCH_3), 39.6 ($\text{C}=\text{OCHCH}_3$), 63.2 (CHN), 75.2 (CHOH), 82.2 ($\text{C}(\text{CH}_3)_2$), 126.9 (phenyl CH), 128.6 (phenyl CH), 129.1 (phenyl CH), 136.6 (phenyl C), 152.0 ($\text{OC}=\text{O}$), 178.1 ($\text{NC}=\text{O}$); IR (KBr disc) ν_{max} (cm^{-1}): 3471 (O-H), 1774 ($\text{C}=\text{O}$), 1676 ($\text{C}=\text{O}$); HRMS m/z (ES) $[\text{M}+\text{H}]^+$ requires 404.2795, found 404.2797

(*S*)-4-Benzyl-3-((2*S*,3*R*,4*S*)-3-hydroxy-2,4-dimethyl-decanoyl)-5,5-dimethyl-oxazolidin-2-one, (4*S*)-351b

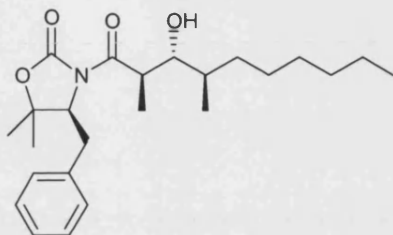


According to general procedure 6.2.19 B, employing (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylene-decanoyl)-5,5-dimethyl-oxazolidin-2-one **350** (50 mg, 0.125 mmol) in DCM (0.5 mL) the crude product was prepared as a colourless oil. Purification by column chromatography afforded (*S*)-4-benzyl-3-((2*S*,3*R*,4*S*)-3-hydroxy-2,4-dimethyl-decanoyl)-5,5-dimethyl-oxazolidin-2-one (*4S*)-**351b** as an off white solid.

mp 78 – 83 °C; $[\alpha]_D^{25} - 14.6^\circ$ (c 1.30, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz): δ 0.88 (3H, m, CH_2CH_3), 0.95 (3H, d, CHCH_3 , $J = 6.8$ Hz), 1.18 (3H, d, $\text{C}=\text{OCHCH}_3$, $J = 7.2$ Hz), 1.26 (8H, m, C_4H_8), 1.37 (3H, s, $\text{C}(\text{CH}_3)_2$), 1.39 (3H, s, $\text{C}(\text{CH}_3)_2$), 1.58 (3H, overlapping m, CHCH_3 and CH_2), 2.49 (1H, broad s, OH), 2.91 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, $J = 14.3, 9.0$ Hz), 3.06 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, $J = 14.3, 4.5$ Hz), 3.62 (1H, dd, CHOH, $J = 7.2, 4.1$ Hz), 3.95 (1H, qd, $\text{C}=\text{OCHCH}_3$, $J = 6.8, 4.1$ Hz), 4.52 (1H, dd, CHN, $J = 9.0, 4.5$ Hz), 7.20 – 7.34 (5H, m, Ph); ^{13}C NMR (CDCl_3 , 75 MHz): δ 11.6 (CH_3), 14.1 (CH_3), 14.9 (CH_3), 22.2 ($\text{C}(\text{CH}_3)_2$), 22.6 (CH_2), 26.8 (CH_2), 28.4 ($\text{C}(\text{CH}_3)_2$), 29.4 (CH_2), 31.8 (CH_2), 33.0 (CH_2), 35.4 (CH_2Ph), 35.6 (CHCH_3), 40.1 ($\text{C}=\text{OCHCH}_3$), 63.3 (CHN), 75.4 (CHOH), 82.2 ($\text{C}(\text{CH}_3)_2$), 126.9 (phenyl CH), 128.6 (phenyl CH), 129.1 (phenyl CH), 136.6 (phenyl C), 152.2

(OC=O), 177.6 (NC=O); IR and mass spec data identical to (*S*)-4-Benzyl-3-((2*S*,3*R*,4*R*)-3-hydroxy-2,4-dimethyl-decanoyl)-5,5-dimethyl-oxazolidin-2-one (*4R*)-**351a**

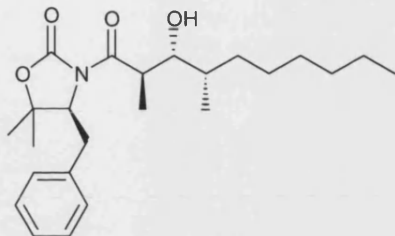
(*S*)-4-Benzyl-3-((2*R*,3*R*,4*R*)-3-hydroxy-2,4-dimethyl-decanoyl)-5,5-dimethyl-oxazolidin-2-one, (*4R*)-362a



According to general procedure 6.2.19 A, employing (*S*)-4-benzyl-3-((*E*)-(2*R*,3*S*)-3-hydroxy-2,4-dimethyl-dec-4-enoyl)-5,5-dimethyl-oxazolidin-2-one **363** (50 mg, 0.125 mmol) in DCM (0.5 mL) (*S*)-4-benzyl-3-((2*R*,3*R*,4*R*)-3-hydroxy-2,4-dimethyl-decanoyl)-5,5-dimethyl-oxazolidin-2-one (*4R*)-**362a** was prepared in 85% *d.e.* as a pale yellow oil.

¹H NMR (CDCl₃, 300 MHz): δ 0.86 (6H, m, CH₂CH₃ and CHCH₃), 1.12 (3H, d, C=OCHCH₃, J = 6.8 Hz), 1.24 (8H, m, C₄H₈), 1.33 (3H, s, C(CH₃)₂), 1.40 (3H, s, C(CH₃)₂), 1.58 (2H, m, CH₂), 2.44 (1H, apparent d, CHCH₃, J = 9.0 Hz), 2.85 (1H, dd, CH_AH_BPh, J = 14.7, 9.8 Hz), 3.18 (1H, dd, CH_AH_BPh, J = 14.7, 3.4 Hz), 3.60 (1H, dt, CHOH, J = 8.7, 3.0 Hz), 4.02 (1H, m, C=OCHCH₃), 4.48 (1H, dd, CHN, J = 10.2, 3.4 Hz), 7.14 – 7.32 (5H, m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 10.8 (CH₃), 14.5 (CH₃), 14.9 (CH₃), 22.4 (C(CH₃)₂), 22.5 (CH₂), 26.7 (CH₂), 28.2 (C(CH₃)₂), 29.5 (CH₂), 32.1 (CH₂), 32.3 (CH₂), 35.0 (CH₂Ph), 36.1 (CHCH₃), 40.1 (C=OCHCH₃), 63.3 (CHN), 75.4 (CHOH), 82.2 (C(CH₃)₂), 126.8 (phenyl CH), 128.6 (phenyl CH), 129.1 (phenyl CH), 136.7 (phenyl C), 152.1 (OC=O), 177.8 (NC=O); IR and mass spec data identical to (*S*)-4-Benzyl-3-((2*S*,3*R*,4*R*)-3-hydroxy-2,4-dimethyl-decanoyl)-5,5-dimethyl-oxazolidin-2-one **351**

(S)-4-Benzyl-3-((2R,3R,4S)-3-hydroxy-2,4-dimethyl-decanoyl)-5,5-dimethyl-oxazolidin-2-one, (4S)-362b

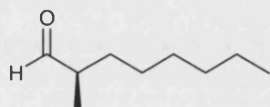


According to general procedure 6.2.19 A, employing (S)-4-benzyl-3-((2R,3S)-3-hydroxy-2-4-methylene-decanoyl)-5,5-dimethyl-oxazolidin-2-one **359** (50 mg, 0.125 mmol) in DCM (0.5 mL) **(S)-4-benzyl-3-((2R,3R,4S)-3-hydroxy-2,4-dimethyl-decanoyl)-5,5-dimethyl-oxazolidin-2-one (4S)-362b** was prepared in 96% *d.e.* as a pale yellow oil.

^1H NMR (CDCl_3 , 300 MHz): δ 0.86 (6H, m, CH_2CH_3 and CHCH_3), 1.20 (3H, d, $\text{C}=\text{OCHCH}_3$, $J = 7.2$ Hz), 1.24 (8H, m, C_4H_8), 1.33 (3H, s, $\text{C}(\text{CH}_3)_2$), 1.40 (3H, s, $\text{C}(\text{CH}_3)_2$), 1.58 (2H, m, CH_2), 2.71 (1H, apparent d, CHCH_3 , $J = 9.8$ Hz), 2.87 (1H, dd, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$, $J = 14.5, 9.6$ Hz), 3.13 (1H, dd, $\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$, $J = 14.5, 3.9$ Hz), 3.39 (1H, m, CHOH), 4.02 (1H, m, $\text{C}=\text{OCHCH}_3$), 4.48 (1H, dd, CHN , $J = 10.2, 3.4$ Hz), 7.13 – 7.32 (5H, m, Ph); ^{13}C NMR (CDCl_3 , 75 MHz): δ 9.4 (CH_3), 14.2 (CH_3), 15.1 (CH_3), 22.2 ($\text{C}(\text{CH}_3)_2$), 22.5 (CH_2), 26.7 (CH_2), 28.3 ($\text{C}(\text{CH}_3)_2$), 29.3 (CH_2), 32.4 (CH_2), 32.5 (CH_2), 35.2 (CH_2Ph), 36.3 (CHCH_3), 39.8 ($\text{C}=\text{OCHCH}_3$), 63.5 (CHN), 75.3 (CHOH), 82.2 ($\text{C}(\text{CH}_3)_2$), 127.4 (phenyl CH), 128.8 (phenyl CH), 129.3 (phenyl CH), 136.1 (phenyl C), 152.4 ($\text{OC}=\text{O}$), 177.8 ($\text{NC}=\text{O}$); IR and mass spec data identical to (S)-4-Benzyl-3-((2S,3R,4R)-3-hydroxy-2,4-dimethyl-decanoyl)-5,5-dimethyl-oxazolidin-2-one **351**

6.2.20 Typical procedure for the retro-aldol reaction

LHMDS (1.1 eq., 1M solution) was added dropwise to a stirred solution of hydrogenated aldol (1 eq.) in toluene at 0 °C. After stirring for 2 hours at 0 °C the reaction was quenched with a few drops of pH 7 buffer, dried (MgSO_4), filtered and evaporated *in vacuo* to afford the crude product which was immediately derivatised to form a more stable compound.

(R)-2-Methyl-octanal, (R)-340a

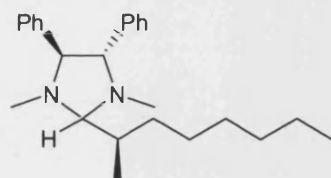
According to general procedure 6.2.20, employing (*S*)-4-benzyl-3-((2*S*,3*R*,4*R*)-3-hydroxy-2,4-dimethyl-decanoyl)-5,5-dimethyl-oxazolidin-2-one (*4R*)-**351a** (15 mg, 0.04 mmol) in toluene (0.7 mL) and LHMDS (0.04 mL, 0.04 mmol) (*R*)-**2-methyl-octanal** (*R*)-**340a** was prepared in 96% *e.e.* (determined by subsequent derivatisation with DMPEDA) as a colourless liquid.

$[\alpha]_D^{25}$ - 17.4 ° (c 8.0, CHCl₃, 96% *e.e.*); ¹H NMR (CHCl₃, 300 MHz): δ 0.84 (3H, t, CH₂CH₃, J = 6.0 Hz), 1.05 (3H, d, CHCH₃, J = 6.2 Hz), 1.10 – 1.37 (8H, m, C₄H₈), 1.64 (2H, m, CH₂CH), 2.24 (1H, m, CHCH₃), 9.55 (1H, s, HC=O); ¹³C NMR (CDCl₃, 75 MHz): δ 14.2 (CH₃), 15.7 (CH₃), 22.9 (CH₂), 26.8 (CH₂), 29.6 (CH₂), 30.4 (CH₂), 32.7 (CH₃), 48.4 (CHCH₃), 203.6 (HC=O); IR (thin film) ν_{max} (cm⁻¹) 1723 (C=O)

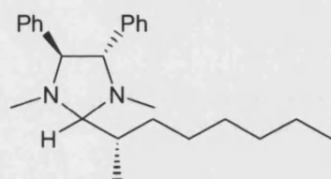
6.2.21 Typical procedure for the derivatisation of aldehydes with DMPEDA

According to procedure 6.2.20, the crude reaction mixture (1 eq.) is redissolved in ether before addition of molecular sieves and DMPEDA (1.1 eq.). After stirring at room temperature for 2 hours the reaction mixture is filtered and evaporated *in vacuo* to yield the crude product which is dissolved in deuterated benzene for ¹H NMR spectroscopy.

(4*S*,5*S*)-1,3-Dimethyl-2-((*R*)-1-methyl-heptyl)-4,5-diphenyl-imidazolidine, (*R*)-**353a**
and (4*S*,5*S*)-1,3-Dimethyl-2-((*S*)-1-methyl-heptyl)-4,5-diphenyl-imidazolidine, (*S*)-**353b**



(*R*)-**353a**



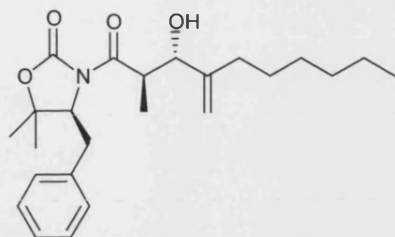
(*S*)-**353b**

^1H NMR (C_6D_6 , 300 MHz): δ 0.99 – 1.38 (26H, m, (*R*)-**353a** C_6H_{13} and (*S*)-**353b** C_6H_{13}), 1.20 (3H, d, (*S*)-**353b** CHCH_3 , $J = 6.8$ Hz), 1.21 (3H, d, (*R*)-**353a** CHCH_3 , $J = 6.8$ Hz), 1.94 (2H, m, (*R*)-**353a** CHCH_3 and (*S*)-**353b** CHCH_3), 2.22 (3H, s, (*R*)-**353a** NCH_3), 2.25 (3H, s, (*S*)-**353b** NCH_3), 2.32 (3H, s, (*S*)-**353b** NCH_3), 2.35 (3H, s, (*R*)-**353a** NCH_3), 3.66 (2H, d, (*R*)-**353a** CHPh and (*S*)-**353b** CHPh , $J = 8.5$ Hz), 3.78 (1H, d, (*S*)-**353b** NCHN , $J = 1.9$ Hz), 3.92 (1H, d, (*R*)-**353a** NCHN , $J = 1.9$ Hz), 4.04 (1H, d, (*R*)-**353a** CHPh , $J = 8.5$ Hz), 4.14 (1H, d, (*S*)-**353b** CHPh , $J = 8.5$ Hz), 6.89 – 7.22 (10H, m, Ar)

6.2.22 Typical procedure for the SuperQuat mediated *anti*-aldol reaction

To a solution of *N*-acylated SuperQuat oxazolidin-2-one (1 eq.) in dry ethyl acetate was added magnesium chloride (0.2 eq.), triethylamine (2 eq.), chlorotrimethylsilane (1.5 eq.) and the desired aldehyde (1.2 eq.). The reaction mixture was stirred at room temperature for 24 hours before the resultant orange slurry was filtered through a plug of silica and washed with diethyl ether. The filtrate was concentrated *in vacuo* before the addition of methanol and trifluoroacetic acid. The mixture was stirred for a further 30 minutes, the solvent was then removed *in vacuo* to afford the crude product.

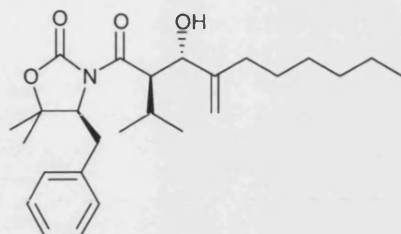
(*S*)-4-Benzyl-3-((2*R*,3*S*)-3-hydroxy-2-methyl-4-methylene-decanoyl)-5,5-dimethyl-oxazolidin-2-one, 359



According to general procedure 6.2.22, employing (*S*)-4-benzyl-5,5-dimethyl-3-propionyl-oxazolidin-2-one **346** (100 mg, 0.38 mmol), magnesium chloride (7.3 mg, 0.076 mmol), triethylamine (0.11 mL, 0.76 mmol), chlorotrimethylsilane (0.07 mL, 0.57 mmol) and 2-methylene octanal **283** (64 mg, 0.46 mmol), the crude product was prepared as a yellow oil. Purification by column chromatography afforded (*S*)-4-benzyl-3-((2*R*,3*S*)-3-hydroxy-2-methyl-4-methylene-decanoyl)-5,5-dimethyl-oxazolidin-2-one **359** (84 mg, 55%) as a colourless oil.

$[\alpha]_D^{25}$ - 40.9 ° (c 1.15, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 0.86 (3H, t, CH₂CH₃, J = 6.8 Hz), 1.13 (3H, d, CHCH₃, J = 6.4 Hz), 1.28 (6H, m, C₃H₆), 1.32 (3H, s, C(CH₃)₂), 1.33 (3H, s, C(CH₃)₂), 1.46 (2H, m, CH₂), 2.00 (1H, m, CH_AH_BC=CH₂), 2.11 (1H, m, CH_AH_BC=CH₂), 2.77 (1H, broad s, OH), 2.83 (1H, dd, CH_AH_BPh, J = 14.7, 9.8 Hz), 3.16 (1H, dd, CH_AH_BPh, J = 14.7, 3.4 Hz), 4.14 (2H, overlapping m, CHOH and CHCH₃), 4.48 (1H, dd, CHN, J = 9.8, 3.4 Hz), 4.91 (1H, m, C=CH_AH_B), 5.02 (1H, apparent s, C=CH_AH_B), 7.16 – 7.31 (5H, m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 14.1 (CH₃), 15.0 (CH₃), 22.3 (C(CH₃)₂), 22.6 (CH₂), 27.9 (CH₂), 28.5 (C(CH₃)₂), 29.2 (CH₂), 31.0 (CH₂), 31.8 (CH₂), 35.1 (CH₂Ph), 40.9 (CHCH₃), 64.1 (CHN), 78.7 (CHOH), 82.3 (C(CH₃)₂), 112.0 (C=CH₂), 126.7 (phenyl CH), 128.7 (phenyl CH), 129.0 (phenyl CH), 137.1 (phenyl C), 149.3 (C=CH₂), 152.8 (OC=O), 177.1 (NC=O); IR and mass spec data identical to (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylene-decanoyl)-5,5-dimethyl-oxazolidin-2-one **350**

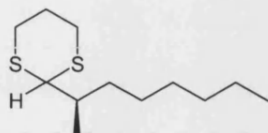
(*S*)-4-Benzyl-3-((2*R*,3*S*)-3-hydroxy-2-isopropyl-4-methylene-decanoyl)-5,5-dimethyl-oxazolidin-2-one, 360



According to general procedure 6.2.22, employing (*S*)-4-benzyl-5,5-dimethyl-3-(3-methylbutyryl)-oxazolidin-2-one **355** (200 mg, 0.69 mmol), magnesium chloride (13 mg, 0.14 mmol), triethylamine (0.19 mL, 1.38 mmol), chlorotrimethylsilane (0.13 mL, 1.04 mmol) and 2-methylene octanal **283** (116 mg, 0.83 mmol), the crude product was prepared as a yellow oil. Purification by column chromatography afforded (*S*)-4-benzyl-3-((2*R*,3*S*)-3-hydroxy-2-isopropyl-4-methylene-decanoyl)-5,5-dimethyl-oxazolidin-2-one **360** (104 mg, 35%) as a colourless oil.

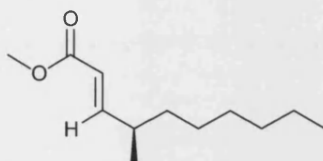
$[\alpha]_D^{25}$ - 11.4 ° (c 0.79, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 0.85 (3H, t, CH₃CH₂, J = 6.8 Hz), 0.93 (3H, apparent dd, CH(CH₃)₂, J = 6.4, 1.3 Hz), 0.96 (3H, d, CH(CH₃)₂, J = 6.8 Hz), 1.10 (3H, d, J = 6.8 Hz), 1.27 (6H, m, C₃H₆), 1.32 (3H, d, J = 4.5 Hz), 1.42 (2H, m, CH₂), 2.07 (2H, m, CH₂C=CH₂), 2.28 (1H, m, CH(CH₃)₂), 2.71 (1H, dd, CH_AH_BPh, J = 14.7, 10.5 Hz), 3.06 (1H, dd, CH_AH_BPh, J = 14.7, 1.8 Hz), 4.15 (1H, dd, CH-ⁱPr, J = 9.8, 3.4 Hz), 4.31 (1H, broad dd, CHOH, J = 10.2, 3.4 Hz), 4.49 (1H, m, CHN), 4.83 (1H, s, C=CH_AH_B), 4.99 (1H, s, C=CH_AH_B), 7.15 – 7.31 (5H, m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 14.5 (CH₃), 20.7, 21.2, 22.6, 23.1, 28.2, 29.4, 32.2, 32.9, 35.6 (CH₂Ph), 50.8 (CH-ⁱPr), 64.2 (CHN), 73.3 (CHOH), 82.2 (C(CH₃)₂), 109.9 (C=CH₂), 127.2 (phenyl CH), 129.1 (phenyl CH), 129.4 (phenyl CH), 137.6 (phenyl C), 151.1 (C), 153.2 (C), 177.5 (NC=O); IR and mass spec data identical to (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-isopropyl-4-methylene-decanoyl)-5,5-dimethyl-oxazolidin-2-one **357**

6.2.23 Procedures for the derivatisation of chiral aldehyde 340

2-((*R*)-1-methyl-heptyl)-[1,3]dithiane, 364

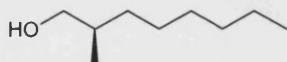
According to general procedure 6.2.20, employing (*S*)-4-benzyl-3-((2*S*,3*R*,4*R*)-3-hydroxy-2,4-dimethyl-decanoyl)-5,5-dimethyl-oxazolidin-2-one (*4R*)-**351a** (150 mg, 0.372 mmol) in toluene (7.5 mL) and LHMDs (0.41 mL, 0.409 mmol). The crude mixture was redissolved in DCM (6 mL), cooled to 0 °C before addition of propane-1,3-dithiol (0.06 mL, 0.558 mmol) and boron trifluoride diethyletherate (0.09 mL, 0.744 mmol) and stirring for 1.5 hours. The reaction was quenched with saturated NaHCO₃ and extracted with DCM. The combined organic extracts were washed with NaHCO₃, dried (MgSO₄), filtered and evaporated *in vacuo* to afford the crude product as a yellow oil. Purification by column chromatography afforded **2-((*R*)-1-methyl-heptyl)-[1,3]dithiane 364** (67 mg, 78%) as a yellow oil, with spectroscopic data essentially identical to the literature compound.^[235]

$[\alpha]_D^{25} + 8.0^\circ$ (c 3.00, ether) [lit. + 8.3 ° (c 3.00, ether)]; ¹H NMR (CDCl₃, 300 MHz): δ 0.87 (3H, t, CH₂CH₃, J = 6.8 Hz), 1.07 (3H, d, CHCH₃, J = 6.8 Hz), 1.23 – 1.36 (10H, m, C₅H₁₀), 1.78 – 1.91 (2H, m, CH₂CH₂S), 2.07 – 2.15 (1H, m, CHCH₃), 2.80 – 2.85 (4H, m, SCH₂CH₂CH₂S), 4.14 (1H, d, SCH, J = 4.1 Hz); ¹³C NMR (CDCl₃, 75 MHz): δ 14.1 (CH₃), 17.0 (CH₃), 22.7 (CH₂), 26.4 (CH₂), 27.3 (CH₂), 29.3 (CH₂), 30.9 (CH₂), 31.2 (CH₂), 31.8 (CH₂), 34.0 (CH₂), 38.5 (CHCH₃), 55.7 (SCH)

(*E*)-(*R*)-4-methyl-dec-2-enoic acid methyl ester, 366

According to general procedure 6.2.20, employing (*S*)-4-benzyl-3-((2*S*,3*R*,4*R*)-3-hydroxy-2,4-dimethyl-decanoyl)-5,5-dimethyl-oxazolidin-2-one (*4R*)-**351a** (100 mg, 0.248 mmol) in toluene (5 mL) and LHMDs (0.27 mL, 0.273 mmol). The crude mixture was redissolved in DCM (5 mL) followed by addition of (carbethoxymethylidene)triphenylphosphorane (91 mg, 0.273 mmol) and stirring at room temperature for 16 hours. Evaporation *in vacuo* afforded the crude product as a colourless oil. Purification by column chromatography afforded (*E*)-(*R*)-4-methyl-dec-2-enoic acid methyl ester **366** (45 mg, 92%) as a colourless oil.

$[\alpha]_D^{25}$ - 27.5 ° (c 0.40, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 0.87 (3H, t, CH₂CH₃, J = 6.6 Hz), 1.03 (3H, d, CHCH₃, J = 6.7 Hz), 1.21 – 1.38 (10H, m, C₅H₁₀), 2.28 (1H, m, CHCH₃), 3.72 (3H, s, OCH₃), 5.77 (1H, dd, C=OCH=CH, J = 15.8, 1.1 Hz), 6.86 (1H, dd, C=OCH=CH, J = 15.8, 7.9 Hz); ¹³C NMR (CDCl₃, 75 MHz): δ 14.5 (CH₃), 19.8 (CH₃), 23.0 (CH₂), 27.6 (CH₂), 29.7 (CH₂), 32.2 (CH₂), 36.4 (CH₂), 37.0 (CHCH₃), 51.8 (OCH₃), 119.5 (C=OCH=CH), 155.6 (C=OCH=CH), 167.8 (C=O); IR (thin film) ν_{max} (cm⁻¹): 1728 (C=O); HRMS: m/z (NH₃Cl⁺) [M+NH₄]⁺ requires 216.1958, found 216.1960

(*R*)-2-Methyl-octan-1-ol, 367

According to general procedure 6.2.20, employing (*S*)-4-benzyl-3-((2*S*,3*R*,4*R*)-3-hydroxy-2,4-dimethyl-decanoyl)-5,5-dimethyl-oxazolidin-2-one (*4R*)-**351a** (80 mg, 0.20 mmol) in toluene (4 mL) and LHMDs (0.22 mL, 0.22 mmol). The crude mixture was redissolved in diethylether (2 mL) before addition of borane dimethylsulfide (0.09 mL, 1.00 mmol) and stirring at room temperature for 4 hours. The reaction was quenched with a couple of drops of saturated NH₄Cl and filtered through celite. Evaporation *in vacuo* afforded the crude

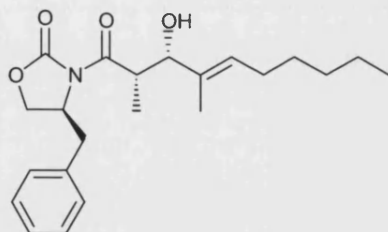
product as a yellow oil. Purification by column chromatography afforded (*R*)-2-methyloctan-1-ol **367** (22 mg, 75%) as a colourless liquid with spectroscopic data essentially identical to the literature compound.^[218]

$[\alpha]_D^{25} + 10.0^\circ$ (c 1.0, CHCl₃) [lit. $+ 10.3^\circ$ (c 1.00 CH₂Cl₂)]; ¹H NMR (CDCl₃, 300 MHz): δ 0.86 (3H, t, CH₂CH₃, J = 7.0 Hz), 0.89 (3H, d, CHCH₃, J = 6.8 Hz), 1.10 (2H, m, CH₂), 1.30 (8H, m, C₄H₈), 1.61 (1H, m, CHCH₃), 1.89 (1H, broad s, OH), 3.38 (1H, dd, CH_AH_BOH, J = 10.4, 6.5 Hz), 3.45 (1H, dd, CH_AH_BOH, J = 10.4, 6.5 Hz); ¹³C NMR (CDCl₃, 75 MHz): δ 14.0 (CH₃), 16.1 (CH₃), 22.6 (CH₂), 26.5 (CH₂), 29.4 (CH₂), 31.7 (CH₂), 33.1 (CH₂), 35.7 (CHCH₃), 68.3 (CH₂OH); IR (thin film) ν_{\max} (cm⁻¹): 3355 (O-H)

6.2.24 Typical procedure for the palladium catalysed isomerisation reaction

To a solution of methylene substituted aldol (1 eq.) in DCM was added either 3 mol% palladium on carbon or 3 mol% palladium (II) acetate in one portion under nitrogen. The vessel was sealed and pressured to the required pressure with hydrogen gas. The reaction was stirred for 3 hours before filtering and evaporation *in vacuo* to afford the crude product.

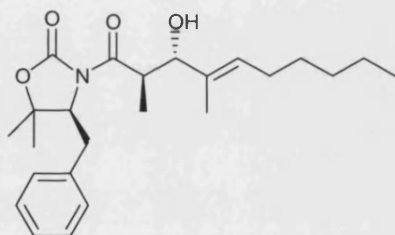
(*S*)-4-Benzyl-3-((*E*)-(2*S*,3*S*)-3-hydroxy-2,4-dimethyl-dec-4-enoyl)-oxazolidin-2-one, **285**



According to general procedure 6.2.24, employing (*S*)-4-benzyl-3-((2*S*,3*S*)-3-hydroxy-2-methyl-4-methylene-decanoyl)-oxazolidin-2-one **282** (50 mg, 0.134 mmol) in IPA (1 mL), palladium on carbon (4.3 mg, 10% Pd, 0.0040 mmol) and 1 bar hydrogen pressure, the crude product is prepared as a colourless oil. Purification by column chromatography afforded (*S*)-4-benzyl-3-((*E*)-(2*S*,3*S*)-3-hydroxy-2,4-dimethyl-dec-4-enoyl)-oxazolidin-2-one **285** (49 mg, 97%) as a colourless oil.

$[\alpha]_D^{25} + 41.7^\circ$ (c 1.2, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz): δ 0.83 (3H, t, CH_2CH_3 , $J = 6.8$ Hz), 1.13 (3H, d, CHCH_3 , $J = 7.2$ Hz), 1.19 - 1.35 (6H, broad m, $(\text{CH}_2)_3$), 1.55 (3H, s, CCH_3), 1.99 (2H, m, $\text{C}=\text{CHCH}_2$), 2.74 (2H, m, $\text{CH}_A\text{H}_B\text{Ph}$ and OH), 3.21 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, $J = 13.6, 3.4$ Hz), 3.93 (1H, qd, CHCH_3 , $J = 6.8, 3.8$ Hz), 4.15 (2H, m, CH_2O), 4.30 (1H, d, CHOH , $J = 3.0$ Hz), 4.63 (1H, m, CHN), 5.50 (1H, apparent tt, $\text{C}=\text{CH}$, $J = 7.4, 1.3$ Hz), 7.13 - 7.32 (5H, broad m, Ph); ^{13}C NMR (CDCl_3 , 75 MHz): δ 10.5 (CH_3), 13.3 (CH_3), 14.0 (CH_3), 22.5 (CH_2), 27.5 (CH_2), 29.1 (CH_2), 31.5 (CH_2), 37.7 (CH_2Ph), 40.4 (CHCH_3), 55.3 (CHN), 66.1 (CH_2O), 75.3 (CHOH), 126.6 ($\text{CH}=\text{C}$), 127.4 (phenyl CH), 128.9 (phenyl CH), 129.4 (phenyl CH), 133.2 (C), 135.1 (C), 153.00 ($\text{OC}=\text{O}$), 177.0 ($\text{NC}=\text{O}$); IR (thin film) ν_{max} (cm^{-1}): 3393 (O-H), 1780 ($\text{C}=\text{O}$), 1709 ($\text{C}=\text{O}$); HRMS: m/z (ES) $[\text{M}+\text{Na}]^+$ requires 396.2145, found 396.2135

(*S*)-4-Benzyl-3-((*E*)-(2*R*,3*S*)-3-hydroxy-2,4-dimethyl-dec-4-enoyl)-5,5-dimethyl-oxazolidin-2-one, 363

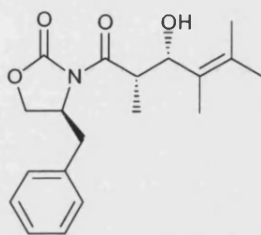


According to general procedure 6.2.24, employing (*S*)-4-benzyl-3-((2*R*,3*S*)-3-hydroxy-2-methyl-4-methylene-decanoyl)-5,5-dimethyl-oxazolidin-2-one **359** (100 mg, 0.25 mmol) in IPA (2 mL), palladium on carbon (8.0 mg, 10% Pd, 0.0075 mmol) and 5 bar hydrogen pressure, the crude product is prepared as a colourless oil. Purification by column chromatography afforded (*S*)-4-benzyl-3-((*E*)-(2*R*,3*S*)-3-hydroxy-2,4-dimethyl-dec-4-enoyl)-5,5-dimethyl-oxazolidin-2-one **363** (97 mg, 97%) as a colourless oil.

$[\alpha]_D^{25} - 15.3^\circ$ (c 1.00, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz): δ 0.87 (3H, t, CH_2CH_3 , $J = 6.8$ Hz), 1.04 (3H, d, CHCH_3 , $J = 6.4$ Hz), 1.28 (3H, s, $\text{CH}_3\text{C}=\text{CH}$), 1.36 (6H, m, C_3H_6), 1.60 (3H, s, $\text{C}(\text{CH}_3)_2$), 1.66 (3H, s, $\text{C}(\text{CH}_3)_2$), 2.03 (2H, m, $\text{CH}_2\text{CH}=\text{C}$), 2.47 (1H, broad s, OH), 2.88 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, $J = 14.7, 9.8$ Hz), 3.21 (1H, dd, $\text{CH}_A\text{H}_B\text{Ph}$, $J = 14.7, 3.4$ Hz), 4.08 (2H, overlapping m, CHCH_3 and CHOH), 4.52 (1H, dd, CHN , $J = 9.8, 3.4$ Hz), 5.44 (1H, apparent td, $\text{C}=\text{CH}$, $J = 7.2, 1.5$ Hz), 7.19 - 7.34 (5H, m, Ph); ^{13}C NMR (CDCl_3 , 75 MHz):

δ 10.8 (CH₃), 14.0 (CH₃), 14.8 (CH₃), 22.2 (C(CH₃)₂), 22.5 (CH₂), 28.5 (C(CH₃)₂), 29.0 (CH₂), 29.5 (CH₂), 31.5 (CH₂), 35.2 (CH₂Ph), 40.9 (CHCH₃), 64.1 (CHN), 81.3 (CHOH), 81.9 (C(CH₃)₂), 126.7 (phenyl CH), 128.6 (phenyl CH), 129.0 (phenyl CH), 130.1 (C=CH), 134.0 (C=CH), 137.2 (phenyl C), 152.2 (OC=O), 177.1 (NC=O); IR (thin film) ν_{\max} (cm⁻¹): 3516 (O-H), 1779 (C=O), 1700 (C=O); HRMS: m/z (ES) [M+H]⁺ requires 402.2639, found 402.2637

(S)-4-Benzyl-3-((2S,3S)-3-hydroxy-2,4,5-trimethyl-hex-4-enoyl)-oxazolidin-2-one, 380



According to general procedure 6.2.24, employing (S)-4-benzyl-3-((2S,3S)-3-hydroxy-2,5-dimethyl-4-methylene-hexanoyl)-oxazolidin-2-one **378** (50 mg, 0.14 mmol) in IPA (1.5 mL), palladium (II) acetate (1.0 mg, 0.0042 mmol), at 5 bar hydrogen pressure the crude product is prepared as a grey oil. Purification by column chromatography afforded **(S)-4-benzyl-3-((2S,3S)-3-hydroxy-2,4,5-trimethyl-hex-4-enoyl)-oxazolidin-2-one 380** (20 mg, 40%) as a colourless oil.

$[\alpha]_D^{25} + 27.4^\circ$ (c 0.73, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 1.34 (3H, d, CHCH₃, J = 6.8 Hz), 1.65 (6H, s, C=C(CH₃)₂), 1.71 (3H, s, CH₃C=C), 2.76 (1H, dd, CH_AH_BPh, J = 13.6, 9.4 Hz), 3.23 (1H, dd, CH_AH_BPh, J = 13.6, 3.4 Hz), 4.03 (1H, apparent pentet, CHCH₃, J = 6.8 Hz), 4.16 (2H, m, CH₂O), 4.60 (1H, m, CHN), 4.87 (1H, dd, CHOH, J = 6.8, 3.4 Hz), 7.18 – 7.37 (5H, m, Ph); ¹³C NMR (CDCl₃, 75 MHz): δ 13.0 (CH₃), 13.7 (CH₃), 20.2 (CH₃), 21.2 (CH₃), 37.7 (CH₂Ph), 41.9 (CHCH₃), 55.3 (CHN), 66.0 (CH₂O), 71.9 (CHOH), 127.4 (phenyl CH), 128.9 (C=C), 128.9 (phenyl CH), 129.4 (phenyl CH), 129.6 (C=C), 135.1 (phenyl C), 152.9 (OC=O), 176.1 (NC=O); IR (thin film) ν_{\max} (cm⁻¹): 3518 (O-H), 1780 (C=O), 1695 (C=O); HRMS: m/z (ES) [M+NH₄]⁺ requires 349.2122, found 349.2117

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